NDA 022496, S009
EXPAREL
Assessment of Efficacy Data of Studies Submitted in Support of sNDA

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Overview of Presentation

- Background of the sNDA application
- Efficacy
  - Pivotal studies
- Statistical overview – Katherine Meaker, M.S.
- Efficacy
  - Possible etiologies for femoral nerve block study failure
  - Supportive studies
  - Opioid sparing
- Pharmacokinetics – Suresh Naraharisetti, Ph.D.
- Safety
  - Previous observations
  - New data
  - Local anesthetic systemic toxicity (LAST)
  - Conclusions

General Comments

- Clinical studies using infiltration demonstrate that the PK profile of EXPAREL varies by anatomical site of injection. Systemic absorption of bupivacaine from EXPAREL is dependent upon total dose, route, vascularity at the site of administration.
- Efficacy results from local exposure of bupivacaine from EXPAREL
- Safety is based on local effects and systemic bupivacaine exposure

Initial NDA Approval

- Studies submitted with outcomes for infiltration
  - 5 Phase 2 active-controlled studies with bupivacaine HCl
  - 3 Phase 3 active-controlled studies with bupivacaine HCl
  - 2 Phase 3 placebo-controlled studies with no active comparator
- Studies submitted with outcomes for nerve block
  - 1 Phase 2 active-controlled study with bupivacaine HCl (ankle block)

Phase 2, Active-Controlled Infiltration Studies* – Exparel and Bupivacaine (1)

Name	Objective	Study Drugs	N	Population	Outcome
SKY0402-C-201	Efficacy Safety PK	EXPAREL 155 mg EXPAREL 200 mg EXPAREL 266 mg EXPAREL 310 mg Bupivacaine HCl 0.25% (40 mL)	12 12 12 14 26	Postsurgical pain inguinal hernia repair	No clinical or statistical difference
SKY0402-C-207	Efficacy Safety	EXPAREL 93 mg EXPAREL 160 mg EXPAREL 306 mg Bupivacaine HCl 0.25% (42 mL)	25 24 25 24	Postsurgical pain inguinal hernia repair	No clinical or statistical difference
SKY0402-C-208	Efficacy Safety Bioavail-ability PK	EXPAREL 133 mg EXPAREL 266 mg EXPAREL 395 mg EXPAREL 532 mg Bupivacaine HCl 0.25% (60 mL)	28 25 26 25 34	Postsurgical pain total knee Arthroplasty (TKA)	No clinical or statistical difference
SKY0402-C-209	Efficacy Safety	EXPAREL 67 mg EXPAREL 200 mg EXPAREL 166 mg Bupivacaine HCl 0.25% (30 mL)	24 25 25 26	Postsurgical pain hemorrhoidectomy	No clinical or statistical difference

*Studies were randomized and double-blinded

Phase 2, Active-Controlled Infiltration/Nerve Block Studies*– Exparel and Bupivacaine (2)

Name	Objective	Study Drugs	N	Population	Outcome vs Bupivacaine
SKY0402-C-210	Efficacy Safety	EXPAREL 133 mg EXPAREL 266 mg Bupivacaine HCl 0.375% Instillation in implant pocket (20 mL)	20 20 40	Postsurgical pain breast augmentation	No clinical or statistical difference
SKY0402-C-203	Efficacy Safety PK	EXPAREL 155 mg EXPAREL 200 mg EXPAREL 310 mg Bupivacaine HCl 0.5% Perineural ankle nerve block (25 mL)	12 12 14 20	Postsurgical pain bunionectomy	No clinical or statistical difference

*Studies were randomized and double-blinded

Study SKY0402-C-210

- Phase 2 study comparing EXPAREL 133 mg and 266 mg to 0.375% BUP for breast augmentation
- 2 control groups matched for volume
- No prespecified primary endpoint
  - Pain intensity scores on a 0-10 numeric scale at rest (NRS-R) and with activity (NRS-A)
    - NRS-R also immediately after wake-up & at 1st opioid request
  - Pain assessments time: 1 - 96 hours
  - Postop opioid use through 96 hours

Phase 3, Active-controlled Infiltration Studies*– Exparel and Bupivacaine (3)

Name	Objective	Study Drugs	N	Population	Outcome vs. bupivacaine
SIMPLE TKA 311	Efficacy Safety	EXPAREL 532 mg Bupivacaine HCl 0.25% Local infiltration (80 mL)	122 123	Postsurgical pain total knee arthroplasty	No clinical or statistical difference
SIMPLE Hemorrhoid-ectomy 312	Efficacy Safety	EXPAREL 266 mg Bupivacaine HCl 0.25% Local infiltration (40 mL)	101 103	Postsurgical pain Hemorrhoid-ectomy	No clinical or statistical difference
SIMPLE Breast Augmentation 315	Efficacy Safety	EXPAREL 532 mg Bupivacaine HCl 0.5% Local administration (20 mL in each pocket; total 40 mL)	66 70	Postsurgical pain breast augmentation	No clinical or statistical difference

*Studies were randomized and double-blinded

sNDA Background

- **October 28, 2011**: Exparel was approved
- **May 5, 2014**: sNDA was submitted and the proposed indication was postsurgical analgesia via nerve block
  - Study 402-C-322
    - Did not meet primary efficacy endpoint
  - Study 402-C-323
    - Met primary efficacy endpoint, however, failed to adequately address safety
      - Median Tmax > 72 hours
      - Plasma [BUP] during cardiac and neurologic adverse events
      - Cardiac safety data
      - Onset and duration of FNB
- **February 27, 2015**: Complete Response

Study 322: Intercostal Nerve Block – Posterolateral Thoracotomy

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group study
- 191 subjects were randomized 1:1 to receive Exparel 266 mg or placebo
  - Study drug was administered under direct visualization by surgeon prior to surgical site closure
- 7 subjects enrolled in USA sites and 184 enrolled in the European sites (Poland, Georgia, Czech Republic, Bulgaria)

Study 322 Results

Study	Treatment	Treatment Result* [mean (SD)]	P-value
402-C-322	Exparel 266 mg	353.8 (156.5)	0.5598
	Placebo	343.6 (156.41)	

*Primary efficacy endpoint: Area under the curve (AUC) of the pain intensity score (NRS-R) through 72 hours

Study 322: Applicant's Rationale for Failure

- Baseline mean pre-surgical pain scores were lower in Bulgaria and the Czech Republic
- Surgeons performing the block under direct visualization
  - "Pacira believes that both the variable techniques used by the surgeons, who were likely less experienced with administering a nerve block than an anesthesiologist, as well as the imprecise placement that resulted from direct visualization as opposed to ultrasound, both contributed to the failure of study to show efficacy." (Integrated Summary of Efficacy: Section 5.4 Conclusions)
- Block performed in supine position
- Extremely short time to max concentration and variability in comparison to the other studies
  - High vascularity of the intercostal compartment

Study 323: Femoral NB – Total Knee Arthroplasty

- Multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study
- Study was conducted in two parts
  - **Part 1:** Phase 2, dose finding (N = 94 subjects)
    - N= 22 in 67 mg
    - N= 24 in 133 mg
    - N= 24 in 266 mg
    - N= 24 in placebo
  - **Part 2:** Phase 3 (N = 183 subjects)
    - N = 92 in 226 mg
    - N = 91 in placebo

Study 323 Part 2 Pertinent Results

AUC of NRS-R Pain Intensity Scores Through 72 Hours

Statistics	EXPAREL 266 mg (N = 92)	Placebo (N = 91)
Mean	420.3	514.0
SD	168.81	160.04
Median	398.1	518.3
Min, Max	68, 710	175, 710
Geometric LSM[1]	418.9 (16.86)	515.5 (16.95)
Geometric LSM Ratio[2]	-96.5 (23.92)	
95% CI for Ratio[2]	(-144, -49)	
P-value[2]	< 0.0001	

[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.

[2] Difference from placebo.

LMS = Least Square Means

Source: Applicant's Study 402-C-322 Study Report, Table 13, Page 91

Study 323: Secondary Endpoints

- Time to first opioid rescue (median time (hrs))
  - Part 1:
    - EXP 67 mg: 0.49
    - EXP 133 mg: 0.37
    - EXP 266 mg: 1.29
    - PBO: 0.41
  - Part 2:
    - EXP 266 mg: 0.44
    - PBP: 0.43
- Total postsurgical opioid consumption (morphine equivalents)
  - Part 1:
    - EXP 67 mg: 126.7
    - EXP 133 mg: 100.4
    - EXP 266 mg: 106
    - BPO: 124.8
  - Part 2:
    - EXP 266 mg: 93.2
    - PBO: 122.1

****No subjects (in either group) remained opioid free****

sNDA Complete Response Deficiencies

- Failure to adequately characterize efficacy of EXPAREL for proposed indication
  - Only 1 study met primary efficacy endpoint (femoral nerve block)
- Failure to adequately characterize safety for FNB or for broader nerve block indication

sNDA: Current Submission

- New studies
  - Study 402-C-326: Femoral nerve block
  - Study 402-C-327: Brachial plexus nerve block
- Supportive studies
  - Study 1601: Median and ulnar nerve blocks
  - Study 1602: Posterior tibial and deep peroneal nerve blocks

Indications

- Approved indication: for single-dose infiltration into the surgical site to produce **postsurgical** analgesia
- Proposed indication (previous cycle): for local or regional **postsurgical** analgesia when administered into the surgical site or as a nerve block
- Proposed indication (current cycle): for infiltration to produce local anesthesia and as a nerve block to produce regional analgesia

402-C-326:
Femoral Nerve Block (FNB) –TKA

- Multicenter, randomized, double-blind, placebo-controlled study
- Treatment groups randomized in a 1:1:1 ratio to receive:
  - EXPAREL 133 mg (10 mL Exparel + 10 ml normal saline)
  - EXPAREL 266 mg (20 mL Exparel)
  - Placebo (normal saline)
- All subjects received 8 mL of bupivacaine HCl (0.5%) administered in the posterior capsule by the surgeon
- Total bupivacaine dose in each group
  - EXPAREL 133 mg + 40 mg BUP = 173 mg (75 subjects)
  - EXPAREL 266 mg + 40 mg BUP = 306 mg (76 subjects)
  - Placebo + 40 mg BUP = 40 mg (79 subjects)

Key Differences for the FNB Studies

- Study 323
  - Non-opioid analgesics were not permitted through 72 hours
  - No additional bupivacaine HCl
- Study 326
  - All subjects received cyclobenzaprine
  - All subject received acetaminophen/paracetamol PO or IV every 8 hours post-surgically
  - Bupivacaine HCl via posterior capsule

Study 323 versus Study 326 Results

Study Characteristic	402-C-326 (Femoral)	402-C-323 (Femoral)
Primary Endpoint		
AUC of NRS-R or VAS in 72 hours (mean)	EXP 133mg: 254.61 EXP 266mg: 252.98 Placebo: 282.57	EXP 266mg: 420.3 Placebo: 514.0
Secondary Endpoints		
Total Opioid Use (mean morphine EQ)	EXP 133mg: 165.83 EXP 266mg: 176.83 Placebo: 177.39	EXP 266mg: 93.19 Placebo: 122.08
% Opioid-free	EXP 133mg: 0 EXP 266mg: 0 Placebo: 0	Not Ranked
Time to First Opioid (median hours)	EXP 133mg: 3.03 EXP 266mg: 2.87 Placebo: 2.40	EXP 266mg: 0.44 Placebo: 0.43

VAS = Visual Analogue Scale

402-C-327: Brachial Plexus NB – Total Shoulder Arthroplasty or Rotator Cuff Repair (RCR)

- Multicenter, randomized, double-blind, placebo-controlled study
- Subjects received a single 20 mL dose of one of the following into the brachial plexus (interscalene or supraclavicular):
  - EXPAREL 133 mg (10 mL EXPAREL plus 10 mL of NS) – 69 subjects
  - EXPAREL 266 mg (20 mL of EXPAREL) – 15 subjects
  - Placebo (normal saline) – 71 subjects

Study 327: EXPAREL 266 mg

- EXPAREL 266 mg cohort was discontinued after 15 subjects
  - Interim PK data
    - Median Tmax for 133 mg: 48 hours
    - Median Tmax for 266 mg: 60 hours
  - Vandepitte study (Interscalene block)
    - Groups:
      - DRUG: 5 ml of 0.25% bupivacaine (12.5 mg) + by 10 ml of Exparel (133 mg) = **145.5 mg bupivacaine** (N = 26)
      - SOC: 15 ml 0.25% bupivacaine = **37.5 mg bupivacaine** (N = 24)
    - Marginal differences observed between groups and inadequately powered to detect a true difference

Study 327 Results

Study Characteristic	402-C-327
Primary Endpoint	
AUC of VAS in 48 hrs (mean)	133 mg: 134.2 Placebo: 255.3
Secondary Endpoint	
Total Opioid Use in 48 hrs (mean morphine EQ)	133 mg: 24.8 Placebo: 113.2
Subjects Opioid-free in 48 hrs	133 mg: 9 Placebo: 1
Time to First Opioid (median hrs)	133 mg: 4.2 Placebo: 0.6

EXPAREL sNDA 022496
Efficacy Supplement (S-009)

Statistical Review of EXPAREL Efficacy from Nerve-block Studies

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EXPAREL Efficacy from Nerve-block Studies

In all four pivotal nerve block studies, the primary efficacy endpoint was the Area Under the Curve (AUC) of pain intensity during the post-operative in-clinic timeframe.

Pain was recorded using

- 0-10 Numeric Rating Scale – At Rest (NRS-R) or
- 0-10cm Visual Analog Scale (VAS)

For both scales 0 = No pain and 10=Worst Pain

Efficacy Results: AUC Pain 0-72hours

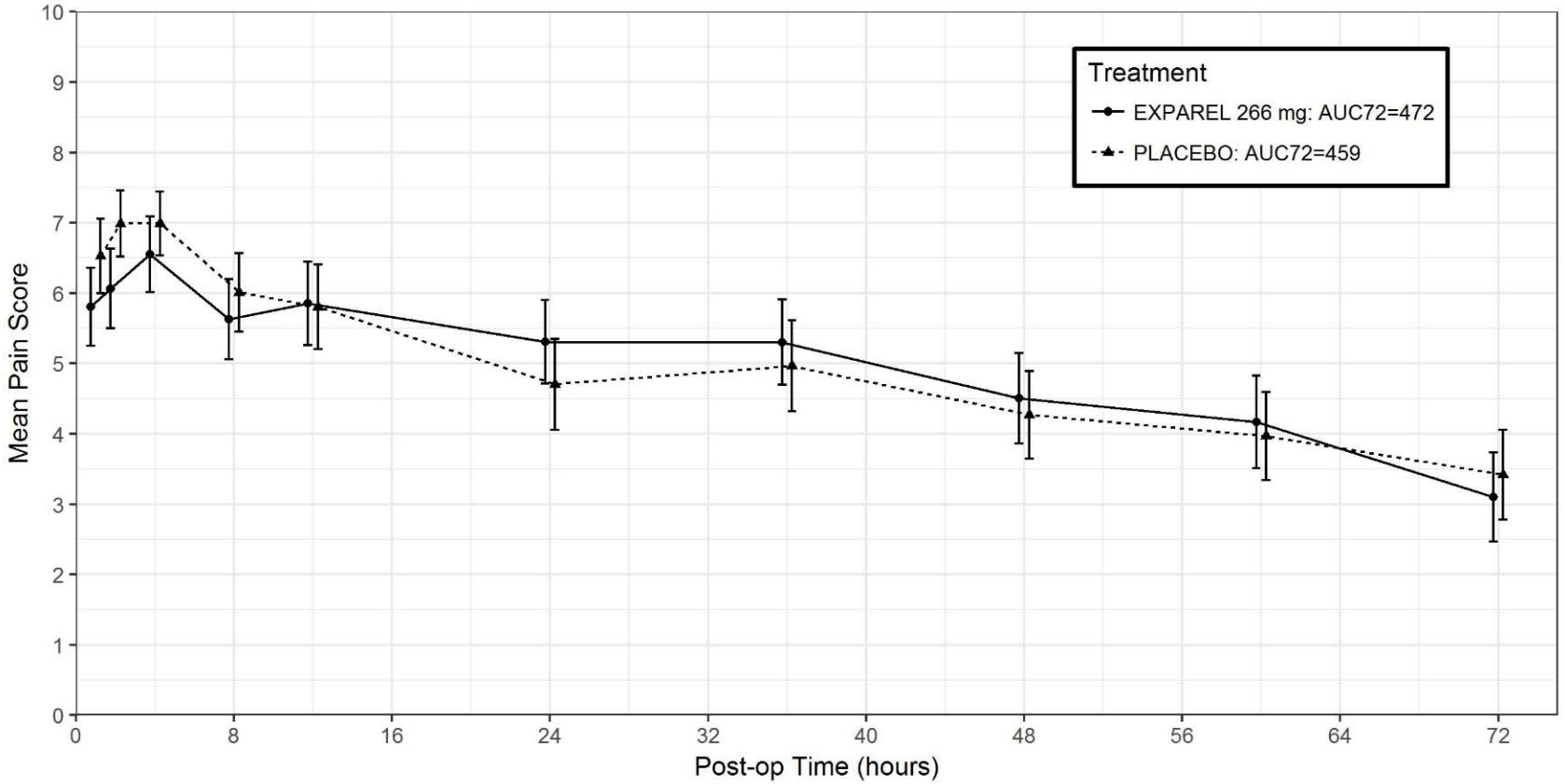
	Nerve Block Pivotal Studies				
	402-C-327 (Brachial Plexus)	402-C-326 (Femoral)		402-C-323 (Femoral)	402-C-322 (Intercostal)
		133 mg	266 mg		
AUC of NRS-R or VAS in 72 hours (mean)	133mg: 218 Placebo: 362	133mg: 260 PLB: 280	266mg: 251 PLB: 280	266mg: 419 Placebo: 516	266mg: 472 Placebo: 459
Difference vs. Placebo LSMEANS (95% CI)	-145 (93, 197)	-20 (-72, 32)	-29 (-80, 23)	-97 (-144, -49)	+13 (-31, 57)
Average Pain over 72 Hours (AUC / 72)	-2.0	-0.3	-0.4	-1.3	+0.2

Least Square Means (LSMEANS); Confidence Interval (CI)

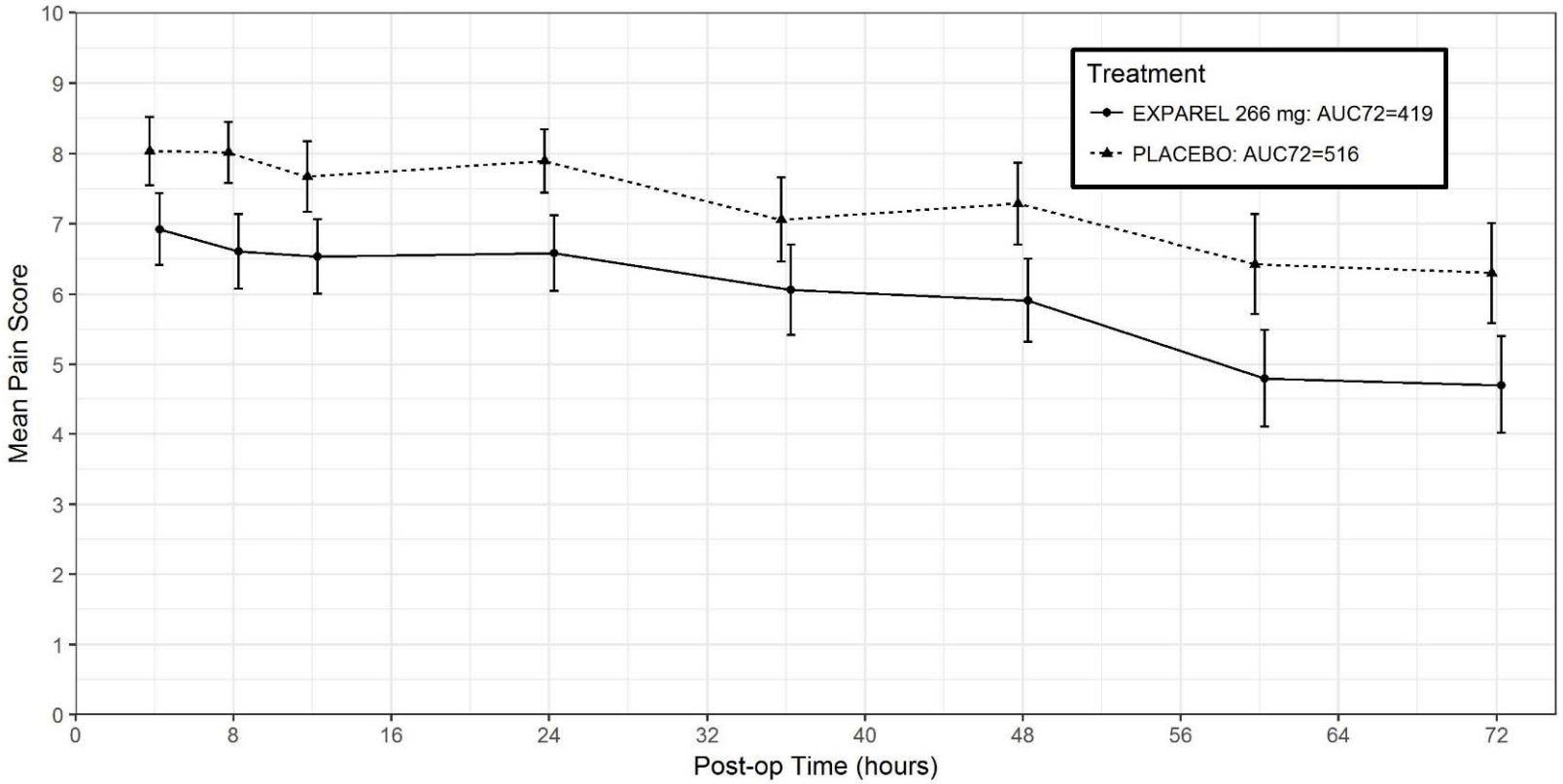
Post hoc analyses of FNB Study 326

- United States vs Rest of World
- Baseline (pre-op) pain
- Prior use of opioid (medical history)
- “poor” posterior capsule injections
- Bupivacaine plasma concentrations
- Proactive pain management by clinic staff
- Double the dose of first rescue in some sites
- Use of incorrect pain scale at some times in some sites

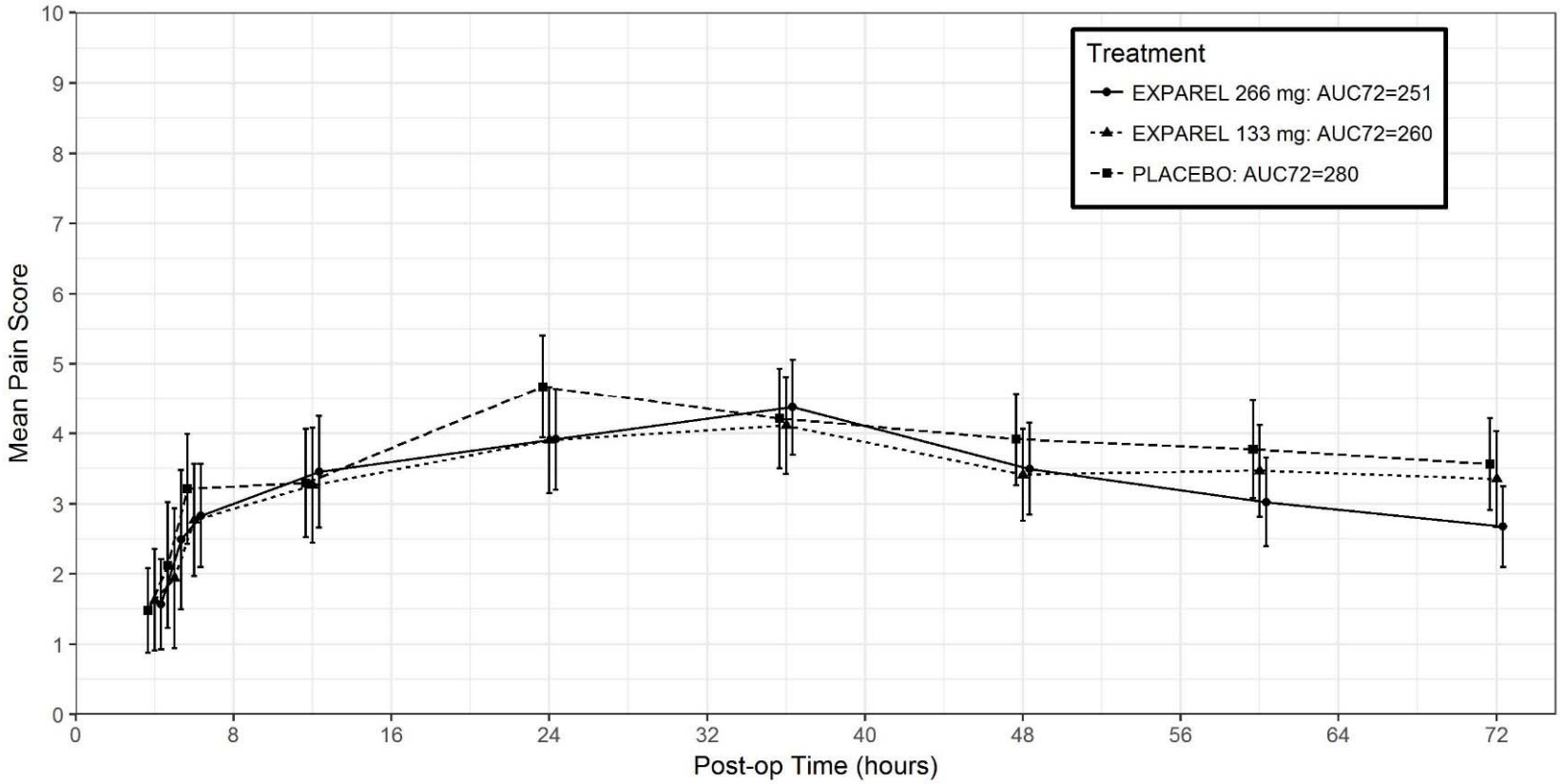
Mean Pain 0-72 hours
Intercostal Nerve Block (322)



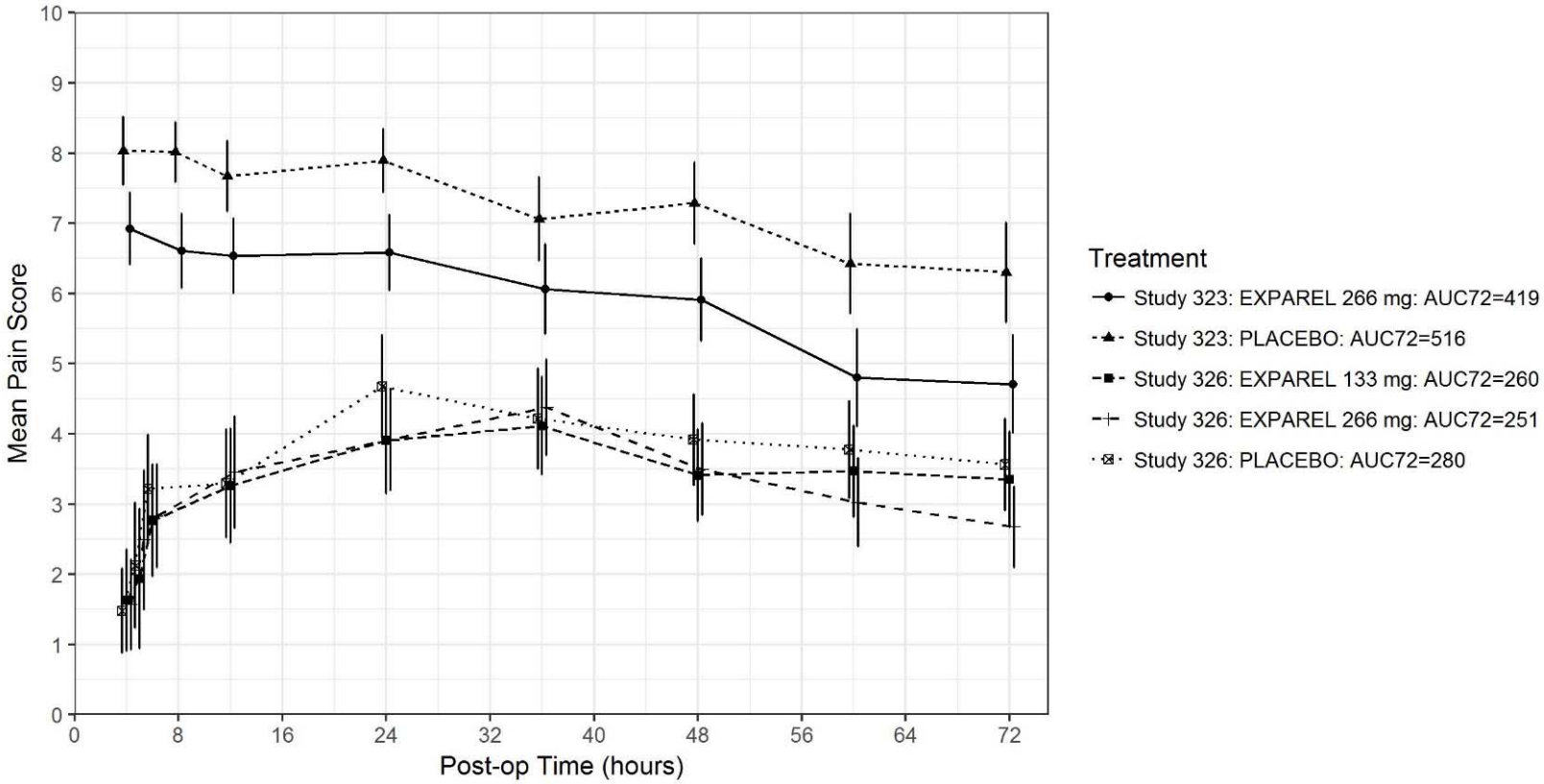
Mean Pain 0-72 hours
Femoral Nerve Block (323)



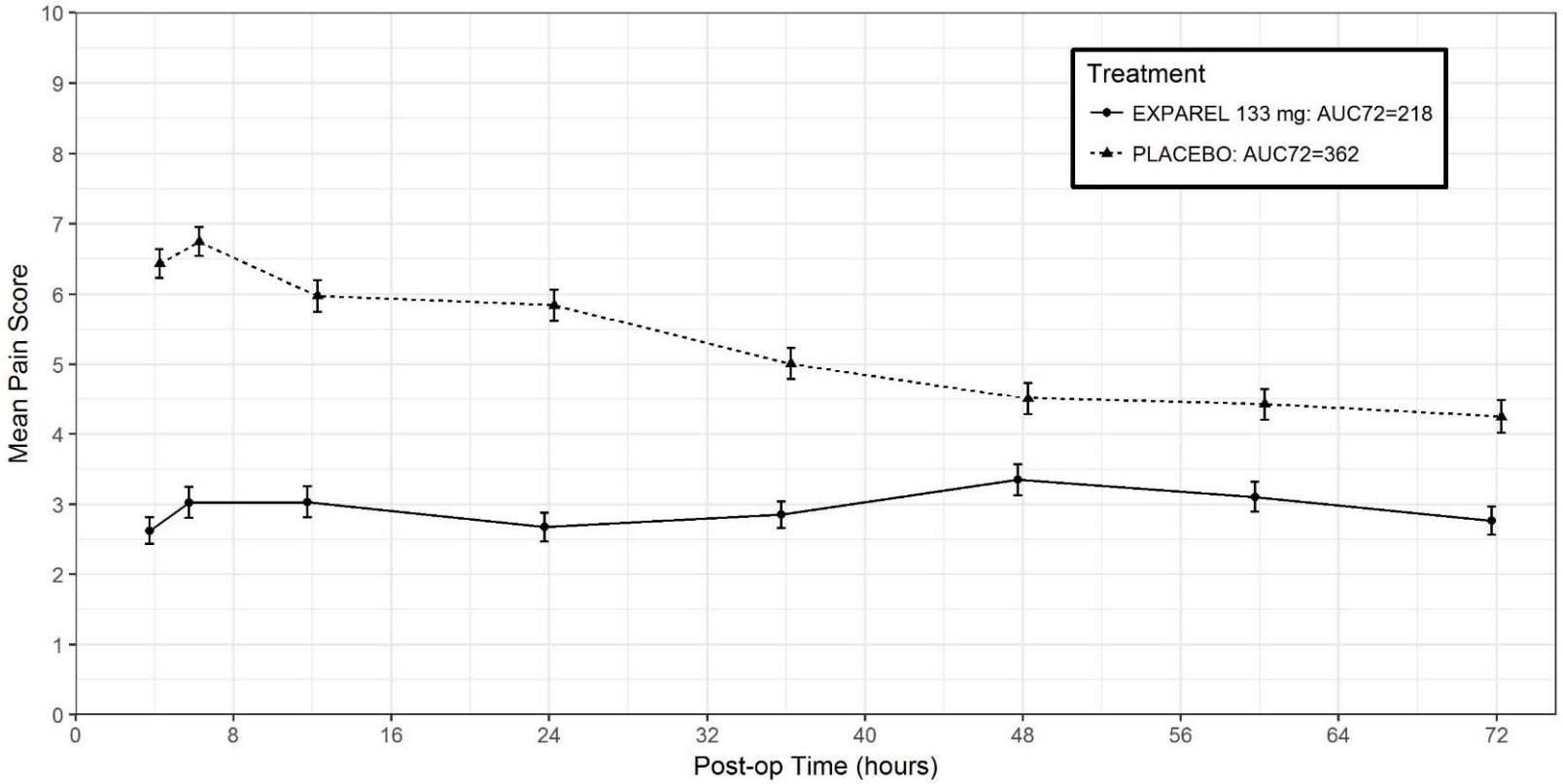
Mean Pain 0-72 hours
Femoral Nerve Block (326)



Mean Pain 0-72 hours
Femoral Nerve Block studies (323 and 326)



Mean Pain 0-72 hours
Brachial Plexus Nerve Block (327)



Opioid Use Outcomes

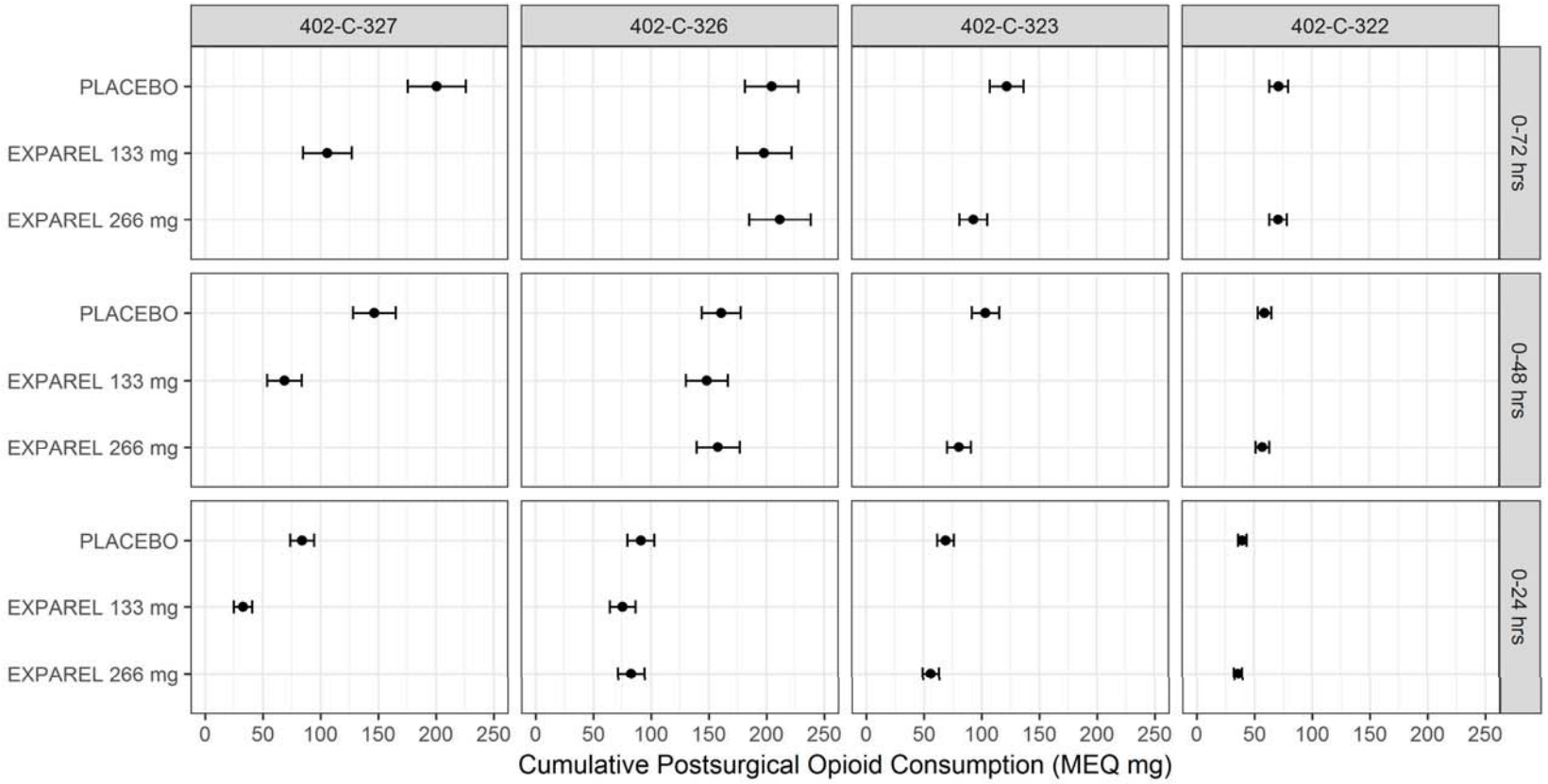
- Total Amount of Opioid Rescue (MEQ dose)
- Proportion of Subjects who Did Not Use Opioid Rescue
- Time to First Opioid Rescue Medication

Total Opioid Consumption 0-72 hrs

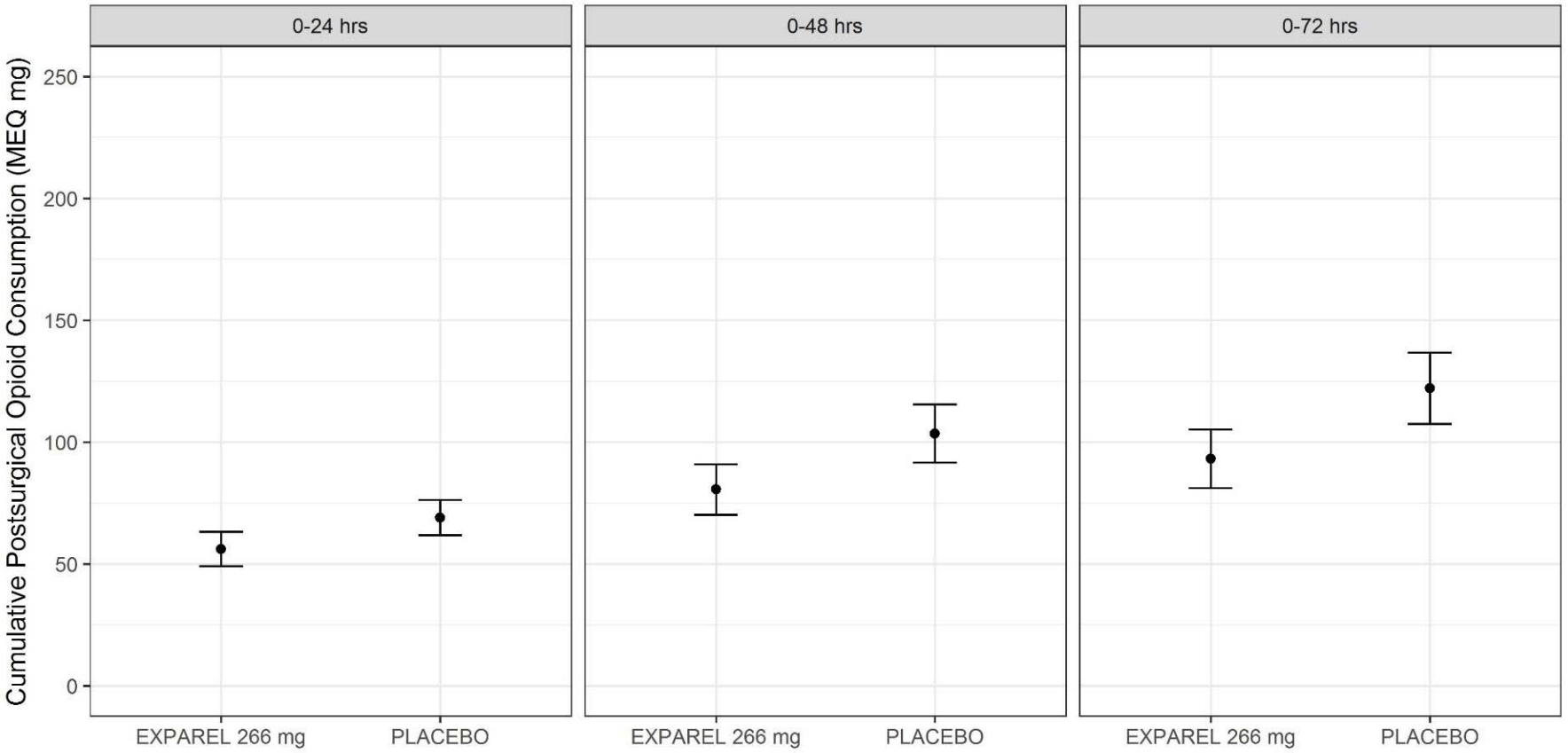
	Nerve Block Pivotal Studies				
	402-C-327 (Brachial Plexus)	402-C-326 (Femoral)		402-C-323 (Femoral)	402-C-322 (Intercostal)
		133 mg +40mg BUP	266 mg +40mg BUP		
Total Opioid Use (mean MEQ mg)	133mg: 52 PLB: 149	133mg: 162 PLB: 178	266mg: 180 PLB: 178	266mg: 76 PLB: 103	266mg: 71 PLB: 71
Diff. vs. placebo	-97 mg *	-16 mg	+2 mg	-27 mg *	0 mg

* P-value < 0.05

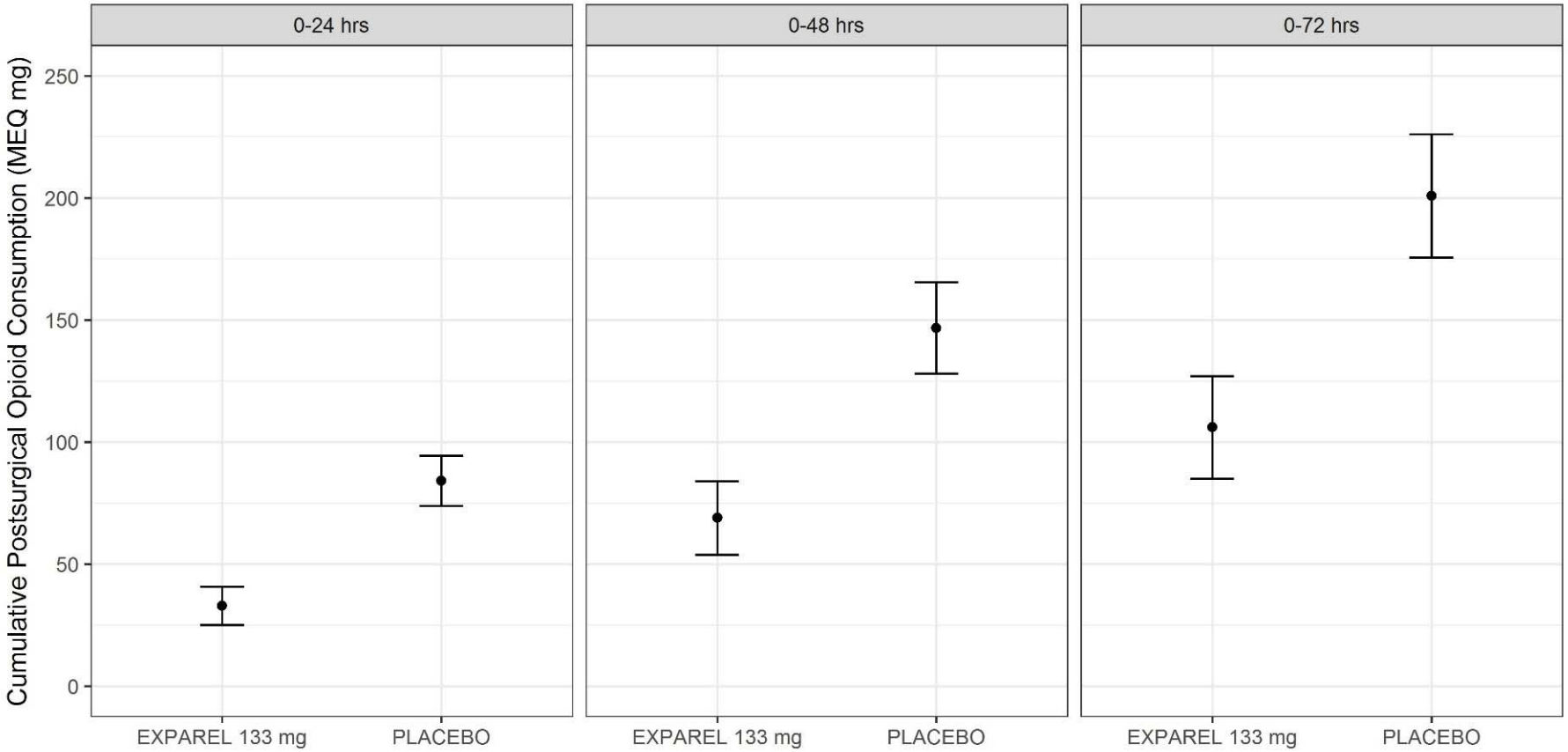
Total Opioid Consumption through 72 hours (MEQ mg)



Total Opioid Consumption through 72 hours (MEQ mg)
Femoral Nerve Block Study 323



Total Opioid Consumption through 72 hours (MEQ mg)
Brachial Plexus Nerve Block Study 327



Proportion of Subjects Who Did Not Use Opioid Rescue through 72 hours

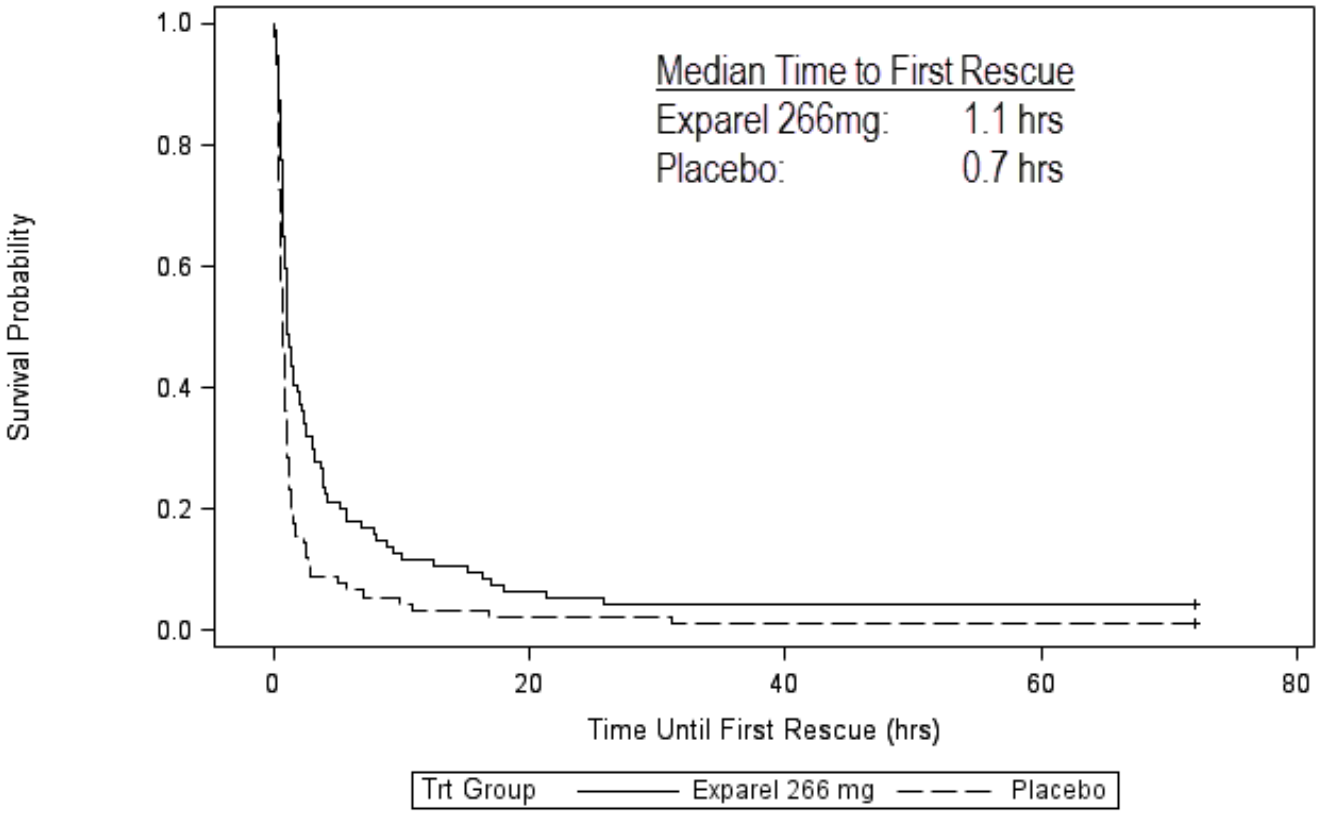
	Nerve Block Pivotal Studies			
	402-C-327 (Brachial Plexus)	402-C-326 (Femoral)	402-C-323 (Femoral)	402-C-322 (Intercostal)
Exparel 266mg		0/76	0/92	4/91 (4%)
Exparel 133 mg	4/69 (6%)	0/75		
Placebo	1/71 (1%)	0/79	0/91	1/91 (1%)

Time to First Opioid Rescue

	Nerve Block Pivotal Studies				
	402-C-327 (Brachial Plexus)	402-C-326 (Femoral)		402-C-323 (Femoral)	402-C-322 (Intercostal)
		133 mg +40mg BUP	266 mg +40mg BUP		
Time to First Opioid (median hours)	133mg: 4.2 PLB: 0.6	133mg: 3.0 PLB: 2.4	266mg: 2.9 PLB: 2.4	266mg: 0.4 PLB: 0.4	266mg: 1.1 PLB: 0.7
Diff. vs. Placebo	3.6 *	-0.6	-0.5	0	-0.4 *

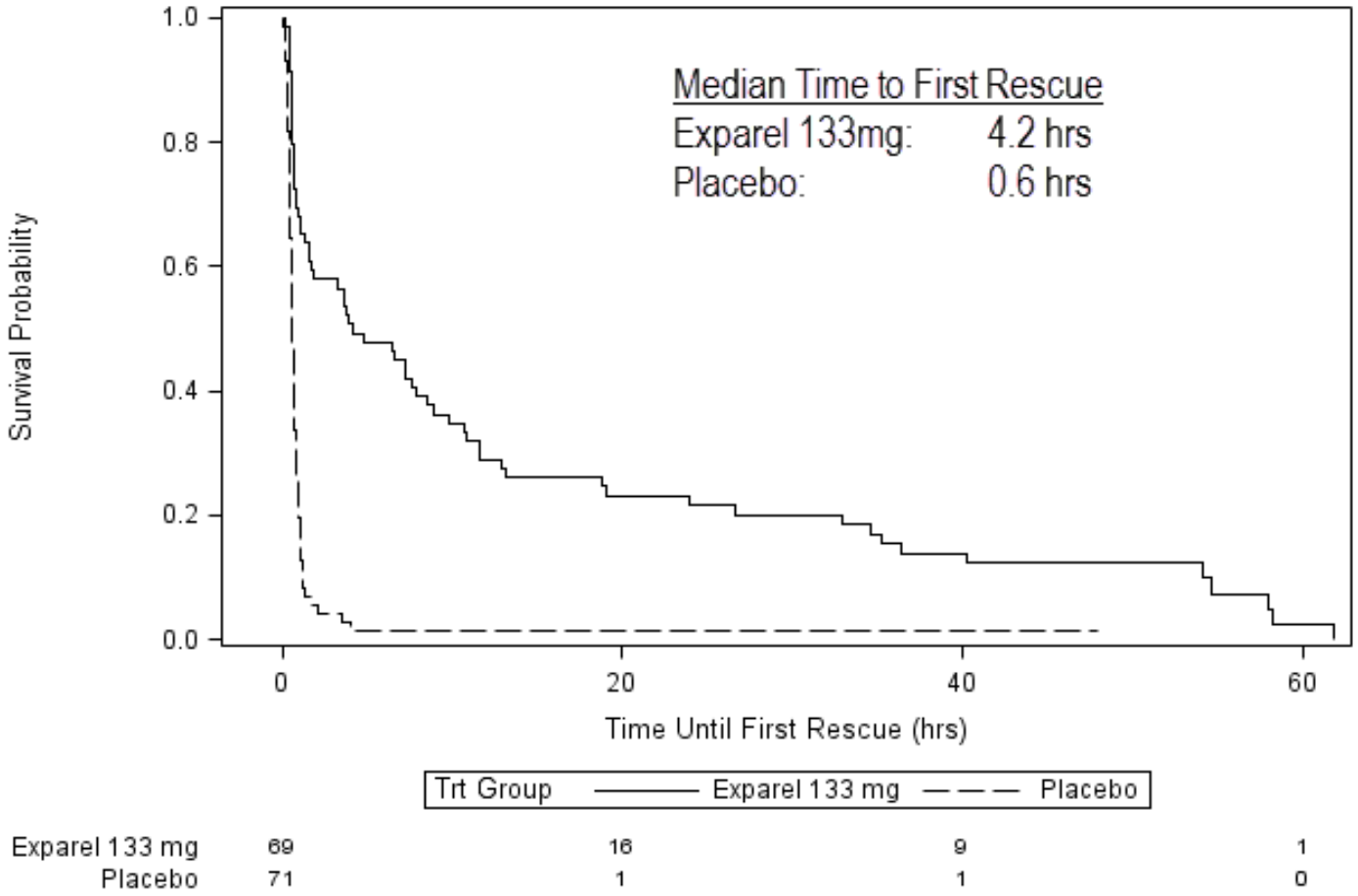
* P-value < 0.05

Time to First Opioid Rescue: Intercostal NB – Study 322



Exparel 266 mg	94	6	4	4	0
Placebo	91	2	1	1	0

Time to First Opioid Rescue: Brachial Plexus NB Study 327



Summary of Statistical Results

	Nerve Block Pivotal Studies				
Endpoints Through 72 hours Post-op	402-C-327 (Brachial Plexus)	402-C-326 (Femoral)		402-C-323 (Femoral)	402-C-322 (Intercostal)
	EXP 133mg v. Placebo	EXP 133mg +40mg BUP v. PLB +40mg BUP	EXP 266mg +40mg BUP v. PLB +40mg BUP	EXP 266mg v. Placebo	EXP 266mg v. Placebo
Post-op Pain Reduction (AUC)	Yes	No	No	Yes	No
Total Opioid Use (mean mg)	Yes	No	No	Yes	No
% Opioid-free	No	No	No	No	No
Time to First Opioid (median hrs)	Yes	No	No	No	Yes

Study 323 Results: Clinical Significance

Study Characteristic	402-C-323 (Femoral)
Primary Endpoint	
AUC of NRS-R in 72 hrs (mean)	266mg: 420.3 Placebo: 514.0
Secondary Endpoint	
Total Opioid Use in 72 hrs (morphine EQ)	266mg: 93.19 Placebo: 122.08
% Opioid-free	Not Ranked
Time to First Opioid (median hrs)	266mg: 0.44 Placebo: 0.43

Study 326: Applicant's Rationale for Failure

- Extended hospital stay required (5 days)
  - Unexperienced investigators
- Technique of FNB
  - Study 323: epidural needle w/ US, catheter placed after drug injection
  - Study 326: standard placement with block needle w/ US
- Differences between US and rest of world (ROW) populations
  - No treatment effect demonstrated even when the US and ROW populations are evaluated separately
  - Similar differences in patient populations in Study 327 (25% of study subjects)

Study 326: Applicant's Rationale for Failure

- Questionable efficacy of posterior capsule injections
  - Belgian subjects had lower BUP levels in PACU "suggesting differences between sites in effectiveness of protocol-prescribed posterior capsule injections." (ISE, Section 4.9)
  - Plasma BUP levels do not correlate with local efficacy
  - Efficacy not met when we repeated the subgroup analysis with all treatment groups

Study 326: Applicant's Rationale for Failure

- Nurses at Belgian site proactively managed use of rescue, instructing subjects to take rescue instead of waiting for subject request and giving double the dose of oxycodone
- Dose of Oxycodone administered:

Statistic	ROW	US
Total # of doses	1777	1341
Max dose (mg)	20	15
Min dose (mg)	4	4
Mean dose (mg)	9.87	8.86
Median dose (mg)	10	10
SD	0.85	2.18

Study 326: Applicant's Rationale for Failure

- Pain was assessed at some ROW sites by a 0 to 10 NRS scale instead of the VAS scale
  - No standardized way to scale the two different pain scores
  - No treatment effect observed even with removal of Belgian study site from analysis

Study 326: Lack of Efficacy?

- Important differences between FNB studies
  - Study 323: no additional local anesthetics; non-opioid analgesics prohibited
  - Study 326: addition of bupivacaine HCl via posterior capsule injections; multimodal analgesic approach
- Historical trend from Applicant's drug development program
  - 9 Phase 2 & 3 studies (not including Study 326) with EXPAREL administered via infiltration or peripheral nerve block conducted with bupivacaine HCl as active control
  - 9/9 failed to demonstrate clinical or statistical difference between EXPAREL and bupivacaine HCl

Study 326: Pertinent Conclusions

- EXPAREL (133 or 266 mg) administered via femoral nerve block has no advantage over bupivacaine HCl administered via the posterior capsule for postoperative pain management in the first 72 hours after total knee arthroplasty
- There were no subjects who remained opioid free

Study 327: Pertinent Results

- Met statistical significance on all primary and secondary endpoints
- No major differences in efficacy between study regions (25% of subjects in Belgium and Denmark)
- No relevant differences in subpopulations
- Opioid free subjects
  - EXPAREL 133 mg: 9/69 subjects (first 48 hours)
  - EXPAREL 133 mg: 4/69 subjects (first 72 hours)
  - Placebo: 1/71 subjects (first 48 and first 72 hours)

FDA U.S. FOOD & DRUG ADMINISTRATION

SUPPORTIVE STUDIES

Study 1601 (Belgium)

- Objective: To compare the duration of sensory blockade with a mixture of EXPAREL + BUP with BUP alone, in subjects undergoing Dupuytren's contracture release after Xiapex® injection
  - 7.5 mL 0.5% BUP to the median & ulnar nerves (total 15 mL) – **75 mg bupivacaine** (N = 16)
  - a mixture of 5 mL EXPAREL 1.3% and 2.5 ml 0.5% BUP per nerve (total 15 mL) – **155 mg bupivacaine** (N = 16)
- Efficacy endpoints:
  - Need for additional local anesthesia to complete treatment for Dupuytren's contracture (finger manipulation to rupture the cords)
  - Worst pain over the early postoperative interval (72 hours)
  - Numbness in the hand over the first postoperative week
- Assessments:
  - Through 7 days to determine duration of postop pain, numbness/ weakness in the surgical hand, side effects, use of pain meds, duration and quality of sleep, and satisfaction with pain control

Study 1601: Results

- Additional local anesthesia to complete Phase 2 of treatment was required by 15 of 16 subjects (94%) who received BUP alone, as compared to only 3 of 16 subjects (20%) who received Exparel/BUP mixture
- Worst pain over the first 72 hours was lower in subjects who received Exparel/BUP mixture vs BUP alone
- Frequency of subjects reporting numbness in BUP alone group decreased rapidly within the first 48 postsurgical hours; in contrast, at least 40% of subjects who received the Exparel/BUP mixture reported numbness through Days 3 and 4
- No major safety events

Study 1602 (Belgium)

- Objective: To evaluate the duration of the analgesic effect achieved following US-guided blocks of the posterior tibial and deep peroneal nerves in subjects undergoing corrective osteotomy for hallux valgus
  - perineural injections of a mixture of BUP 0.5% (2.5 mL) and EXPAREL 1.3% (5 mL) per nerve (15 mL) - **Bupivacaine 155 mg** (N = 12)
  - perineural injections of BUP 0.5% alone (15 mL) – **Bupivacaine 75 mg** (N = 14)
  - General anesthesia (GA) followed by standard multimodal therapy (N = 12)
- Efficacy endpoints:
  - Opioid consumption in the first postoperative week
  - Worst pain over the early postoperative interval
  - Numbness in the foot over the first postoperative week
- Assessments:
  - Through 7 days to determine the duration of postop pain, numbness/weakness in the surgical foot, side effects, use of pain meds, sleep duration and quality, and satisfaction with pain control

Study 1602: Results

- Mean opioid (tramadol odis) consumption in the postoperative period varied among the three study groups
  - 95.8 mg (EXPAREL/BUP mixture)
  - 267.9 mg (BUP alone)
  - 604.2 mg (GA)
- Worst pain over 72 hrs was significantly lower in subjects who received the EXPAREL/BUP mixture OR BUP alone compared to subjects who received GA
- Numbness decreased steadily through Day 4 in BUP alone group whereas numbness appeared to persist through Day 4 in over half of the subjects in EXPAREL/BUP group
- No major safety events

FDA U.S. FOOD & DRUG ADMINISTRATION

OPIOID SPARING

The Opioid Crisis

- Uncontrolled acute pain may be associated with development of chronic pain
- Postsurgical opioid use in some cases may be linked to subsequent persistent use
  - Alam, et.al., 2015
    - First 7 postsurgical days most critical
    - Similar findings with postsurgical NSAID use
  - Brummett, et.al., 2017
    - Persistent postop opioid use NOT entirely due to surgical pain but addressable patient-level predictors (e.g., substance abuse hx, chronic pain, anxiety, mood disorders)
- No data supporting opioid reduction only for the first 72 hrs impacts long-term use
- Unclear there is any additional benefit over existing multimodal approach

Efficacy Summary & Conclusions

- 2 pivotal studies that did not meet primary efficacy endpoint
  - Intercostal Nerve Block (Study 322)
  - Femoral Nerve Block (Study 326)
- 2 pivotal studies that met primary efficacy endpoint
  - Femoral Nerve Block (Study 323)
    - Inadequate characterization of safety
  - Brachial Plexus Nerve Block (Study 327)
- No studies conducted to date demonstrate clinically meaningful opioid sparing, with majority of subjects still requiring significant amount of postoperative opioids

NDA 022496
EXPAREL

Pharmacokinetics (PK) of EXPAREL from Infiltration and Nerve-block Studies

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Office of Clinical Pharmacology
OTS, CDER, FDA

Overview

- EXPAREL- Background
- Infiltration Studies
  - PK of EXPAREL from infiltration studies that supported NDA approval
  - PK of EXPAREL versus BUPIVACAINE in an infiltration procedure
- Nerve-block Studies
  - PK of EXPAREL from nerve-block studies submitted in efficacy supplement
  - PK of EXPAREL versus BUPIVACAINE in a nerve-block (ankle-block) procedure
- Conclusions

The term 'BUPIVACAINE' will be used for 'Immediate-release-BUPIVACAINE HCL' in my presentation

EXPAREL - Background

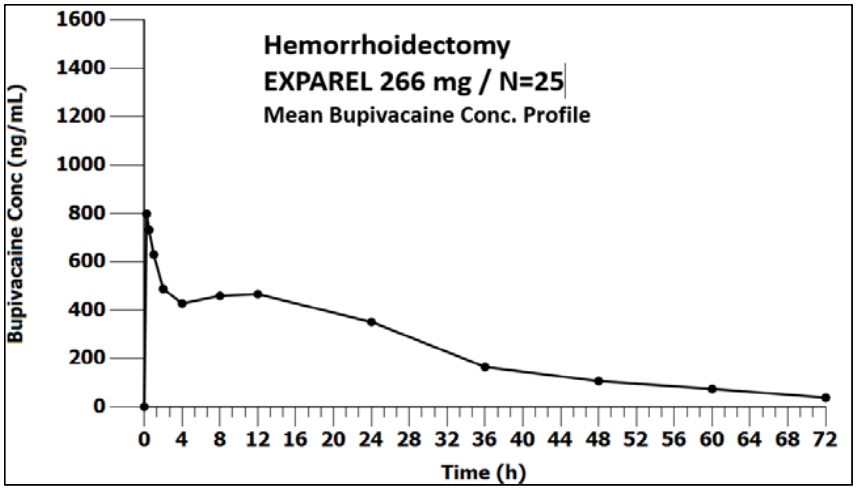
- EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia

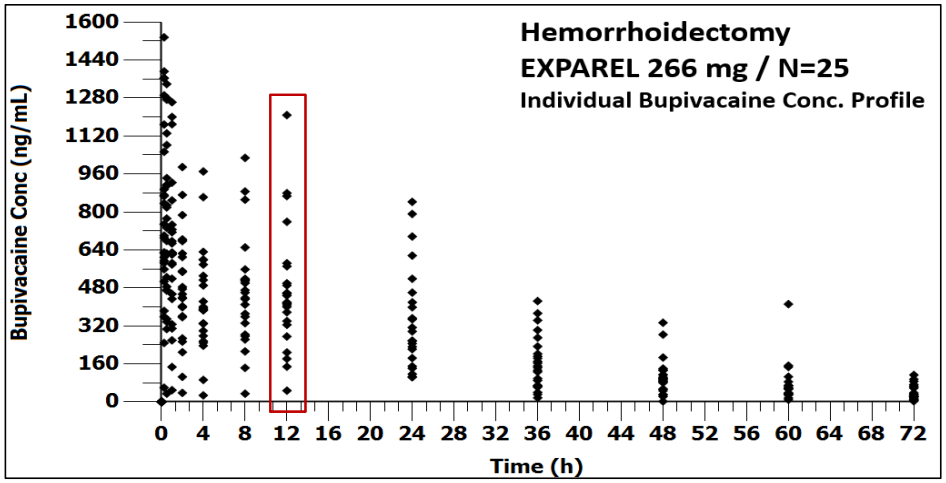
- EXPAREL label notes that:
  - *"Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy"*
  - *"The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site*"

EXPAREL Infiltration Studies: PK

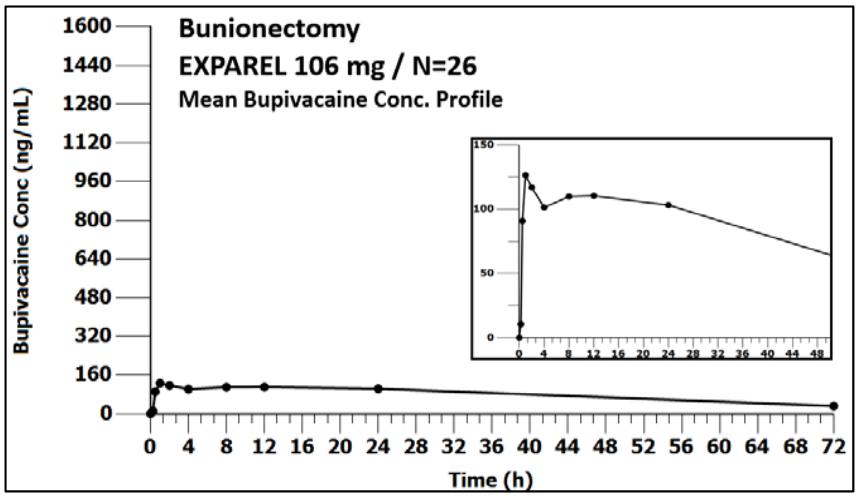
- EXPAREL was approved for surgical procedures, in which the method of administration was infiltration
- Following infiltration procedures supported the NDA approval:
  - Hemorrhoidectomy / Dose: 266 mg
    - PK population of 25 subjects
  - Bunionectomy / Dose: 106 mg
    - PK population of 26 subjects

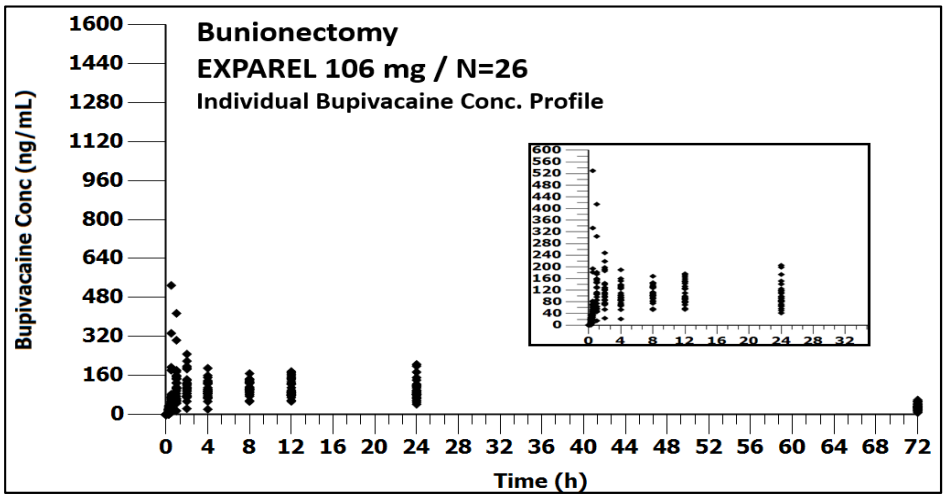
EXPAREL Infiltration Studies: PK Profiles





LOQ: 1ng/mL



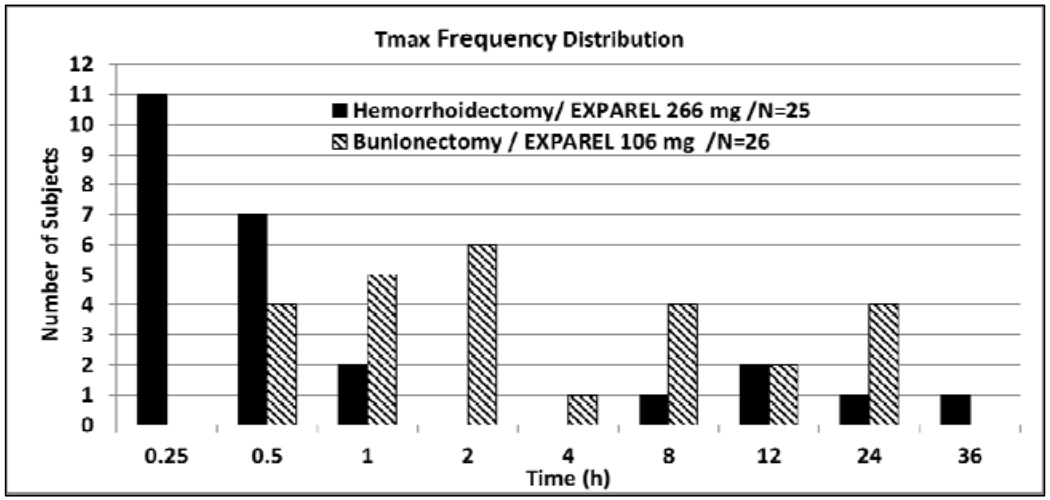


EXPAREL Infiltration Studies: PK Parameters

Parameter Athematic Mean ± SD	Hemorrhoidectomy Study 316 (N=25)	Bunionectomy Study 317 (N=26)
Dose (mg)	266	106
Cmax (ng/mL)	867 ± 353	166 ± 93
Cmax /mg dose	3.3 +1.3	1.6 ± 0.6
Tmax (h)	0.5 [0.25, 36]	2 [0.5, 24]
$AUC_{(0\text{-}t,72\ h)}$ (ng/mL*h)	16867 ± 7868 [a]	5864 ± 2038
AUC(inf) (ng/mL*h)	18289 ± 7569 [a]	7105 ± 2283 [b]
AUC(inf) / mg dose	69 ± 29 [a]	67 ± 22 [b]
t½ (h)	24 ± 39 [a]	34 ± 17 [b]

Tmax- Median (range); [a] N=24 ; [b] N=22

- *Cmax- Maximum Concentration (Conc.)*
- *Tmax- Time to maximum Conc.*
- *AUC: Area under the Conc.-time curve*
- *t1/2- Half-life*

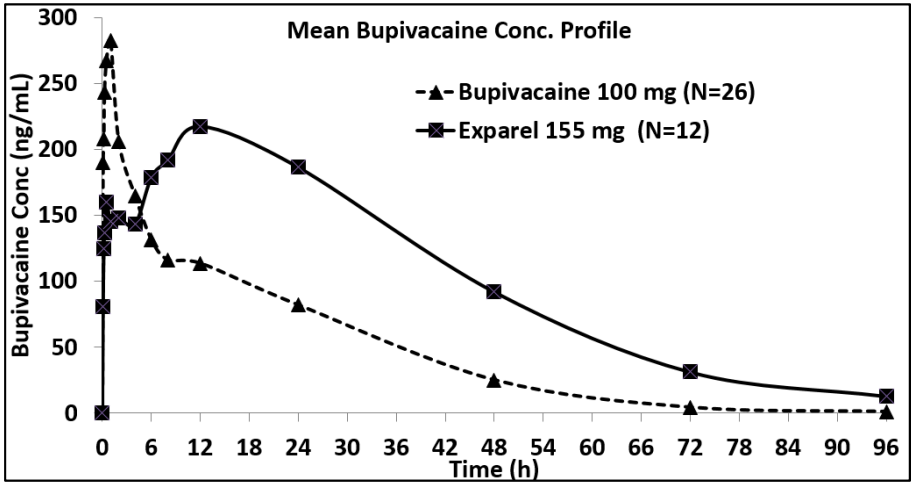


PK Comparison; EXPAREL vs. BUPIVACAINE in an Infiltration Procedure (Inguinal-Hernia-Repair, Study 201)

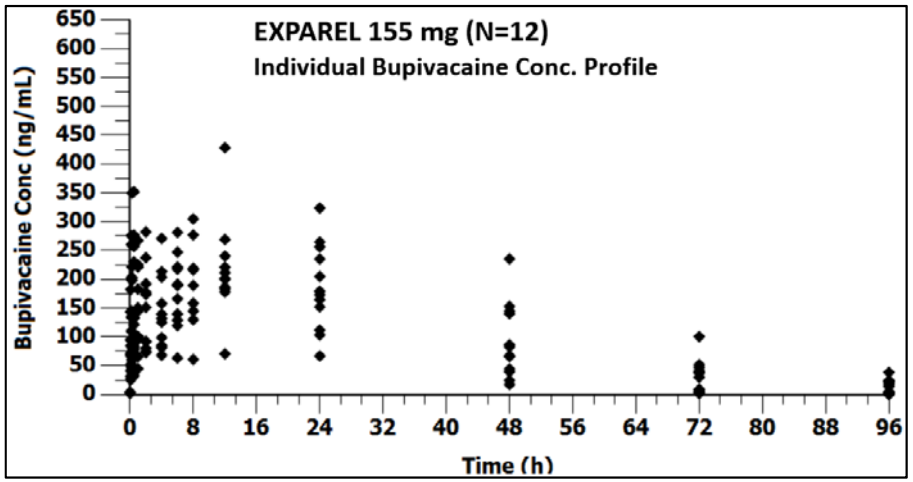
PK Comparison; EXPAREL vs. BUPIVACAINE Inguinal-Hernia-Repair Using Infiltration Procedure (Study 201)

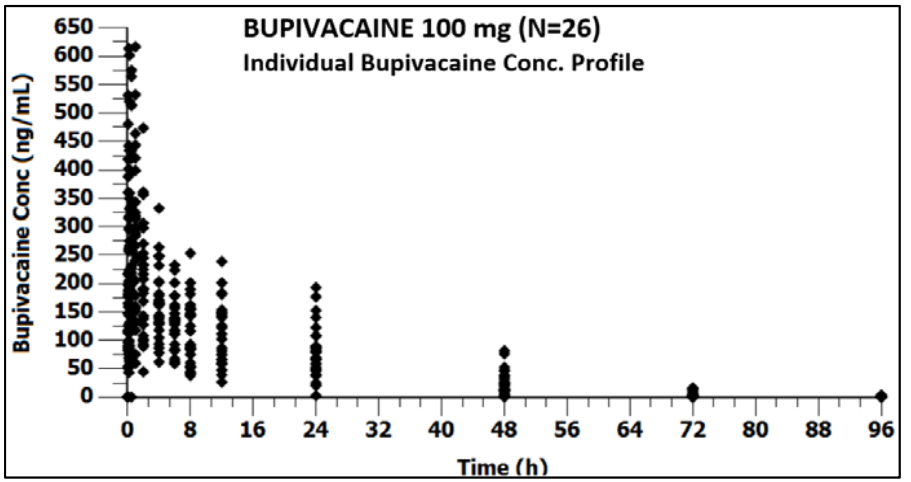
- P2, randomized, double-blind, dose-escalating safety, efficacy, and PK study
  - EXPAREL doses: 155, 200, 266 and 315 mg
  - BUPIVACAINE: 100-mg
- Study drugs were administered via wound infiltration immediately before closure of surgical incision
- PK were compared between:
  - EXPAREL 155 mg (n= 12, cohort 1)
  - BUPIVACAINE 100 mg (n=26, all cohorts)

Inguinal-Hernia-Repair Using Infiltration
EXPAREL 155 mg Vs. BUPIVACAINE 100 mg; PK Profiles

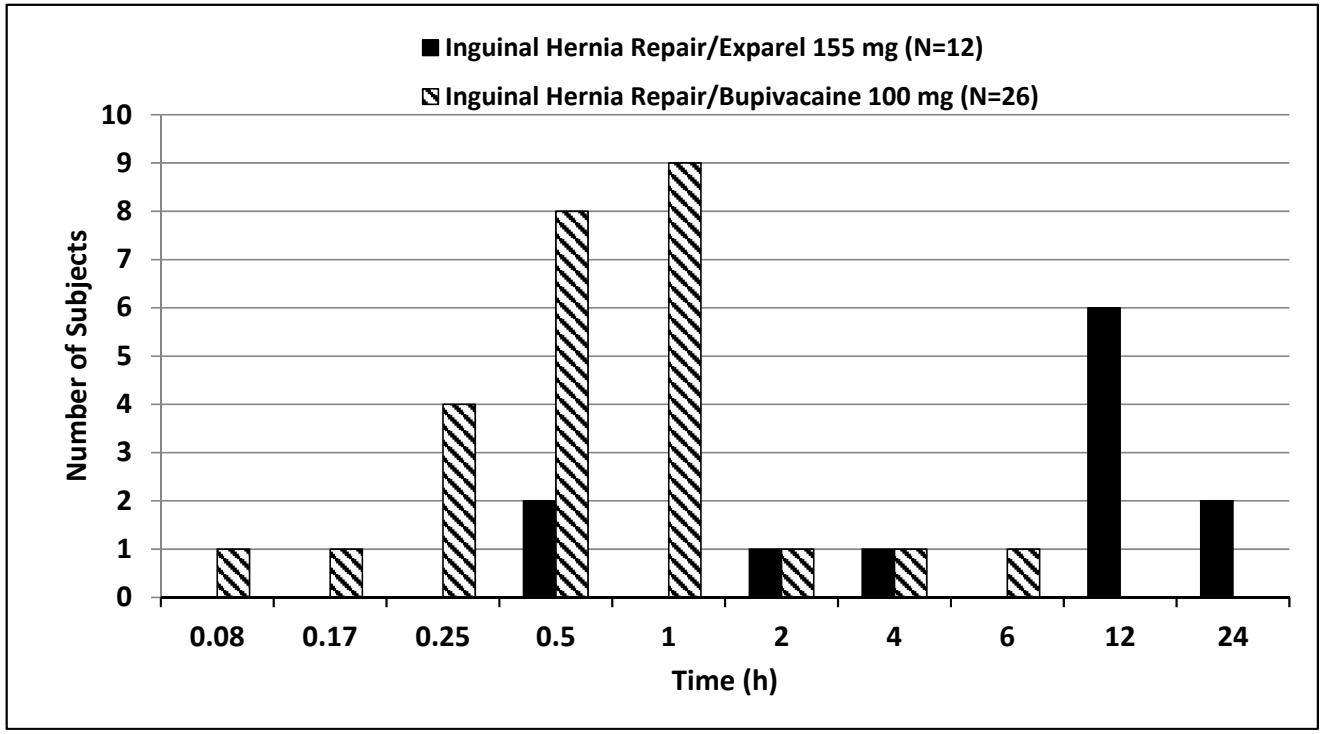


Study # 201
LOQ: 0.1ng/mL





Inguinal-Hernia-Repair Using Infiltration
EXPAREL 155 mg vs. BUPIVACAINE 100 mg
T_{max} Frequency Distribution



Tmax ; Median (range) :

- EXPAREL : 12h (0.5 – 24h)
- BUPIVACAINE : 0.5h (0.08 – 6h)

Study # 201

Nerve-Block Studies; PK

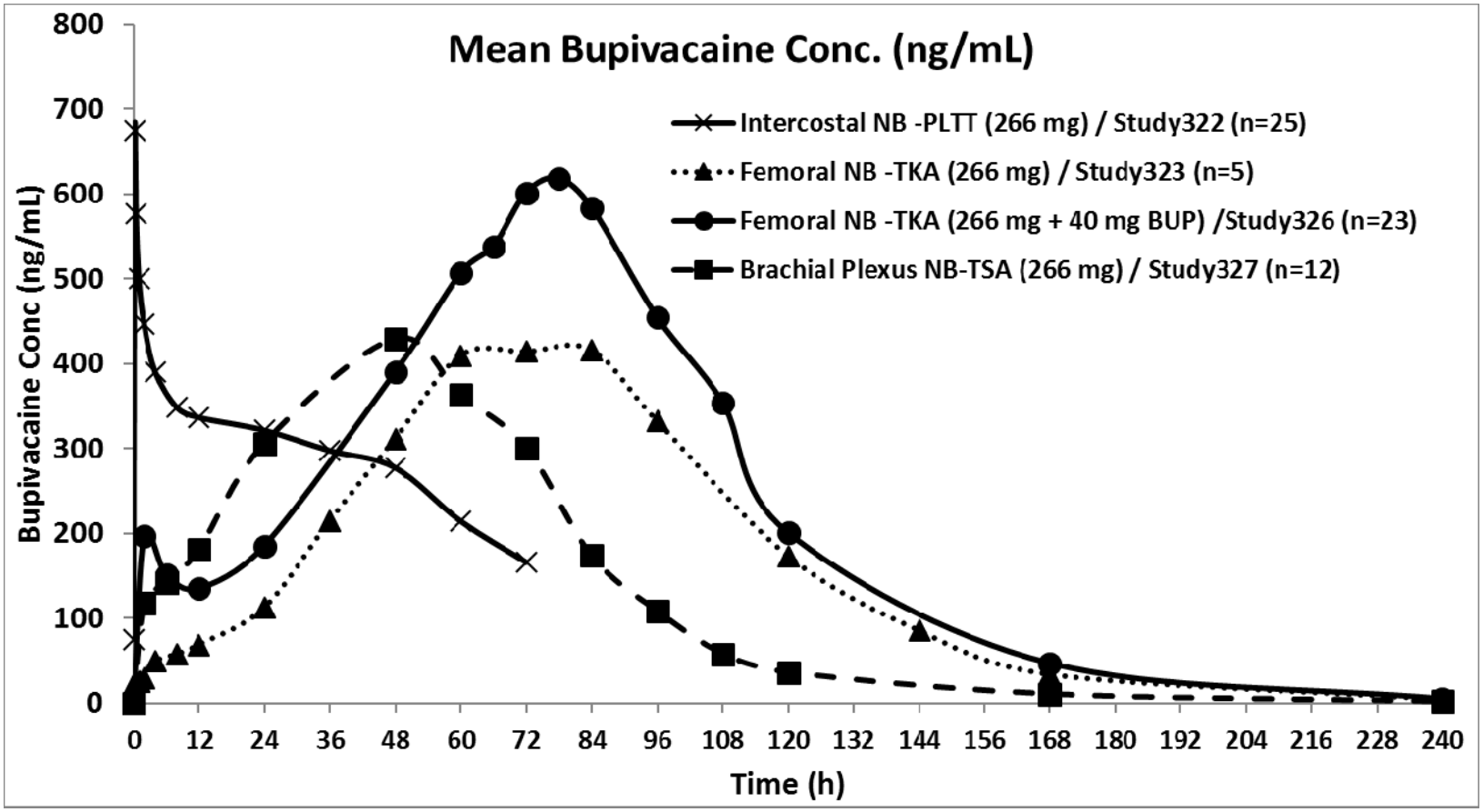
Efficacy Supplement: Phase 3 Nerve-Block Studies; PK

Year	Study # Phase	NB & Procedure	How administered	Doses studied
2014	322 Phase 3	Intercostal nerve-block in postero-lateral thoracotomy	Divided into three equal parts of 88 mg in 6.6 mL and administered to each of three nerve segments (index nerve, nerve above, and nerve below)	• EXPAREL 266 mg

	323 Phase 2/3	Femoral nerve-block in total knee arthroplasty	Single dose injection femoral block under ultrasound guidance	• Part 1: Phase 2, dose finding (with PK)
				  • EXPAREL 67 mg
				  • EXPAREL 133 mg
				  • EXPAREL 266 mg

2017	326 Phase 3	Femoral nerve-block in total knee arthroplasty	Single dose injection femoral block under ultrasound guidance + 40 mg BUPIVACAINE in posterior-capsule	• Placebo + 40 mg BUP (40 mg) • EXPAREL 133 mg + 40 mg BUP (173 mg) • EXPAREL 266 mg + 40 mg BUP (306 mg)
	327 Phase 3	Brachial plexus nerve-block in total shoulder arthoplasty or rotator cuff repair	Deposited into brachial plexus (interscalene or supraclavicular) via syringe under ultrasound guidance	• EXPAREL 133 mg • EXPAREL 266 mg

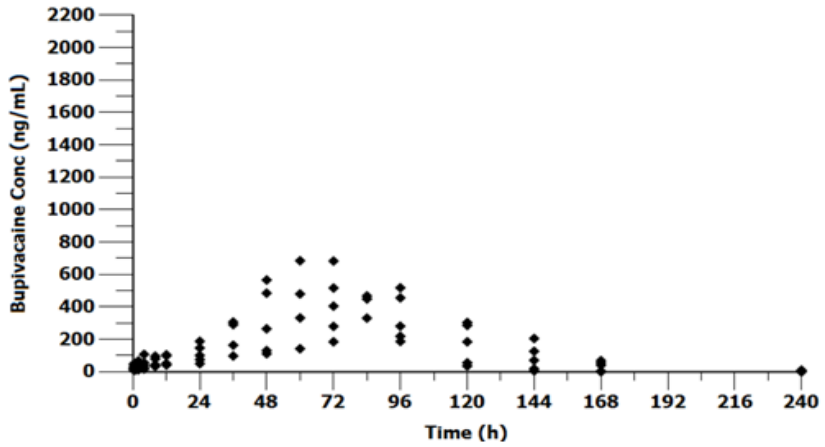
PK Profiles Comparison: 266 mg Exparel in Nerve-Block (NB) studies
(Note: 306 mg for FNB-Study326)



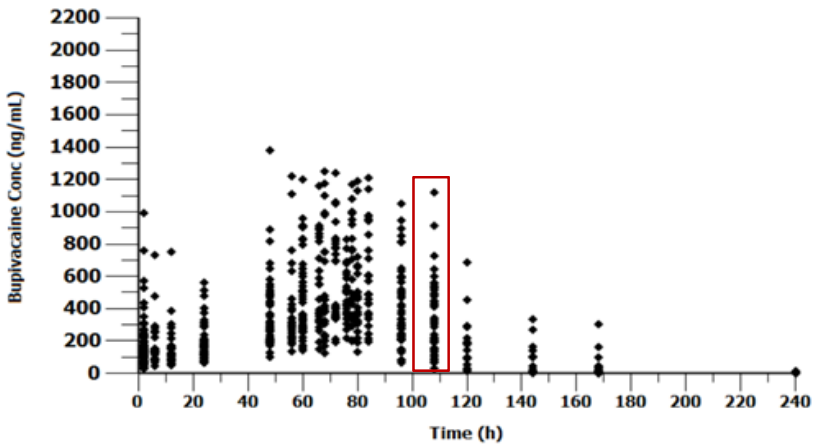
LOQ: 1ng/mL

Individual Conc. Profile Comparison: 266 mg EXPAREL in Nerve-Block Studies

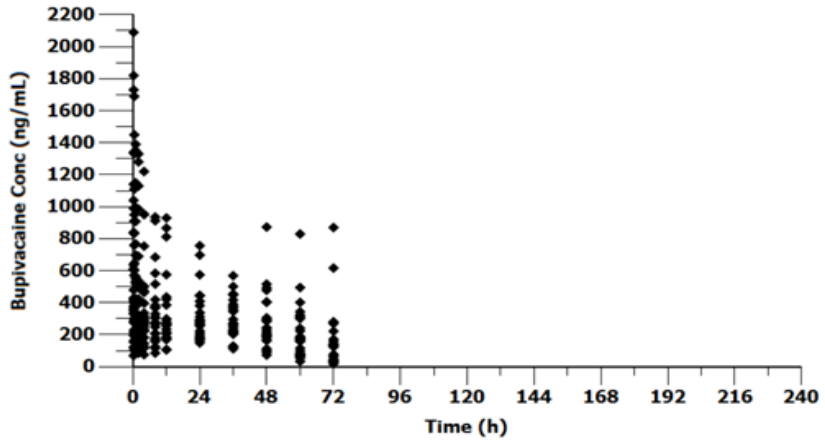
Femoral NB / Study 323/ EXPAREL 266 mg (N=5)



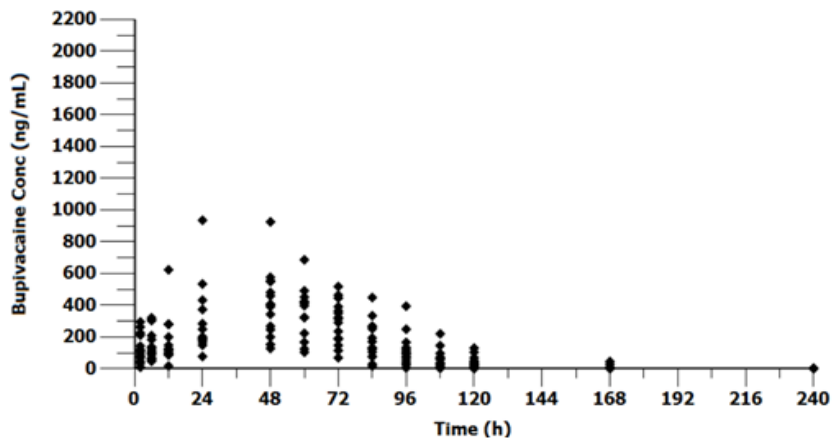
Femoral NB/ Study 326/ EXPAREL 266 mg + 40 mg BUP



Intercostal NB /Study 322/ EXPAREL 266 mg (N=25)



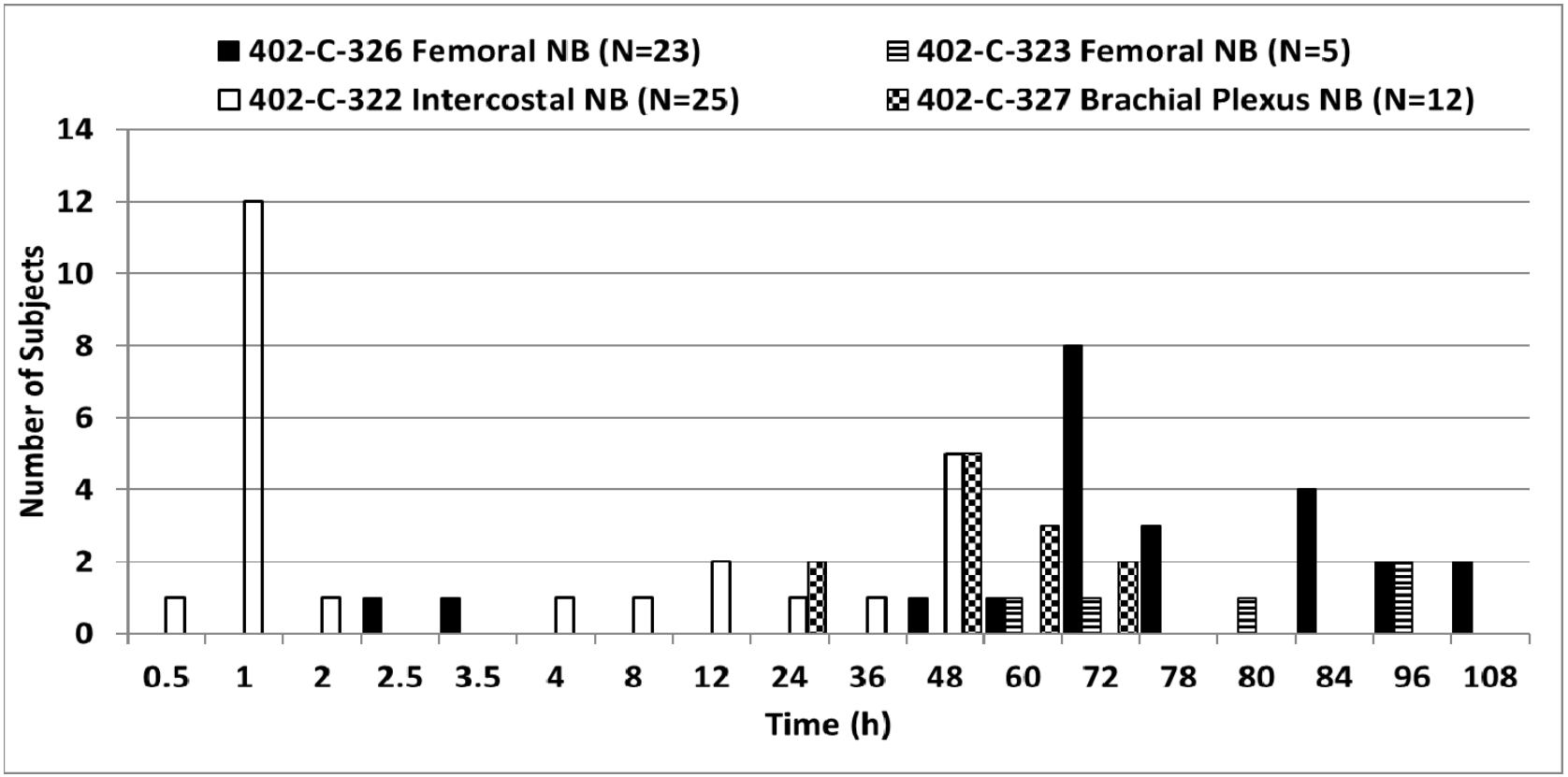
Brachial Plexus NB / Study 327/ EXPAREL 266 mg



(Note: 306 mg for FNB-Study326)

LOQ: 1ng/mL

T_{max} Distribution in 266 mg EXPAREL Nerve-Block Studies



Tmax ; Median (range) :

- Femoral nerve-block (Study 323) : 80 (60 – 96h)
- Femoral nerve-block (Study 326) : 72 (2.5 – 108h)
- Brachial Plexus nerve-block: 48 (24 – 72h)
- Intercostal nerve-block: 01 (0.5- 48 h)

(Note: 306 mg for FNB-Study326)

PK Parameters Comparison for EXPAREL 266 mg; Nerve-Block Studies

Parameter Athematic Mean ± SD	2014 (Study 322) Intercostal NB PL Thoracotomy N=25	2014 (Study 323) Femoral NB- TKA N=5	2017 (Study 326) Femoral NB- TKA N=23	2017 (Study 327) Brachial Plexus NB TSA or Rotator Cuff Repair N=12
Dose (mg) and volume	266 mg in 20 mL	266 mg in 20 mL	266 mg in 20 mL + 40 mg BUP (306 mg)	266 mg in 20 mL
How administered	Divided into three equal parts of 88 mg and administered to three nerve segments (index nerve, nerve above, and nerve below)	Single dose injection femoral block under ultrasound guidance	Single dose injection femoral block under ultrasound guidance + 40 mg BUP	Deposited into brachial plexus (interscalene or supraclavicular) via syringe under ultrasound guidance
PK sampling duration (h)	72	240	240	240
Cmax (ng/mL)	794 ± 510	498 ± 136	743 ± 348	469 ± 194
Cmax / mg dose	2.98 ±1.92	1.87 ± 0.51	2.43 ± 1.13	1.76 ± 0.72
Tmax (h)	1.0 [0.45- 49.5]	80 [60 – 96]	72 [2.5– 108]	48 [24 – 72]
AUC0-t (ng/mL*h)	21203 ± 8650 [1]	34326 ± 5262 [2]	48459 ± 21382 [2]	28857 ± 13351 [2]
AUC(inf) (ng/mL*h)	23264 ± 9210 (n=19)	34496 ± 5297	50514 ± 20978 (n=22)	28991 ± 13449
AUC(inf) / mg dose	88 ± 35 (n=19)	130 ± 20	165 ± 69 (n=22)	109 ± 51
t½ (h)	23 ± 13 (n=19)	19 ± 7	18 ± 17 (n=22)	14 ± 5

[1] AUC(0-t)- 0-72 h; [2] AUC(0-t)- 0-240 h ; Tmax- Median (range)

(Note: 306 mg for FNB-Study326)

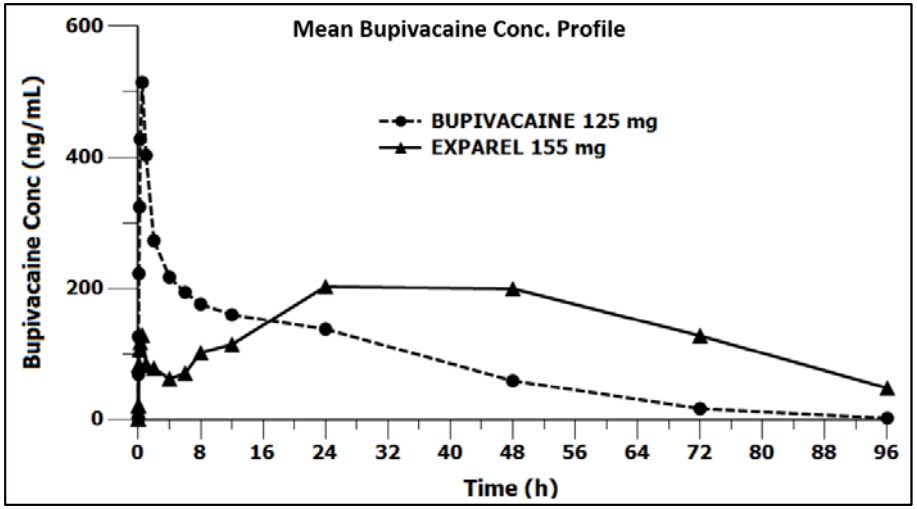
PK Comparison; EXPAREL vs. BUPIVACAINE in a Nerve-Block Procedure (Ankle Block for Bunionectomy, Study 203)

PK Comparison; EXPAREL vs. BUPIVACAINE Ankle Block for Bunionectomy

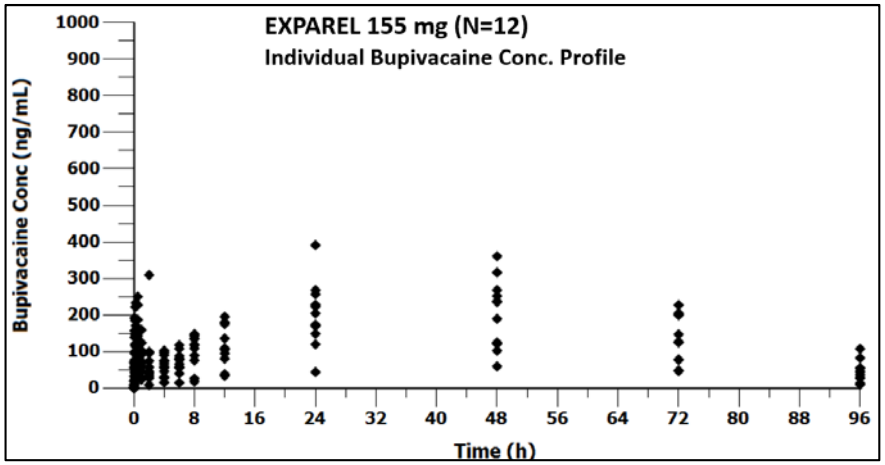
- Phase 2, randomized, double-blind, dose-escalating safety, efficacy, and PK study
  - EXPAREL doses: 155, 200, and 310 mg
  - BUPIVACAINE: 125 mg
- Study drugs were administered via ankle block
- PK were compared between :
  - EXPAREL 155 mg (n= 12)
  - BUPIVACAINE 125mg (n=20)

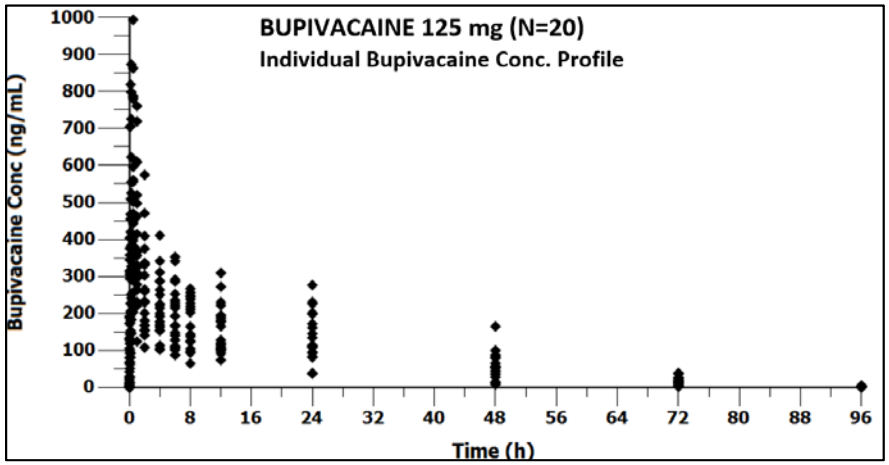
Study # 203

Ankle-Block for Bunionectomy
EXPAREL 155 mg Vs. BUPIVACAINE 125 mg



Study # 203
LOQ: 0.1ng/mL





PK Conclusions

- Variability (scatter) in individual concentrations for EXPAREL appears greater compared to BUPIVACAINE; with BUPIVACAINE in initial time points while for EXPAREL at all time points.
- For the same procedure (either nerve block or infiltration in surgical wound), EXPAREL has longer and variable Tmax, and extended systemic exposure compared to BUPIVACAINE.
- EXPAREL Tmax between nerve block procedures varies widely; ranging 0.5 h to 108 h. Maximum observed Tmax is 108 h (~4.5 days after surgery).
- For different nerve-block studies, for the same dose of EXPAREL, the systemic exposure (AUCinf and Cmax) is different. Hence, predicting systemic exposure from one nerve block procedure to another is difficult for determining duration of systemic-bupivacaine-safety- monitoring.
- PK findings of EXPAREL from nerve block studies are similar to infiltration studies; the rate of systemic absorption of BUPIVACAINE depends on total dose, the route/type of administration, and the vascularity of the administration site.

NDA 022496, S009
EXPAREL
Assessment of Safety Data of Studies Submitted in Support of sNDA

Alla Bazini, MD
Medical Officer
DAAAP, ODE-II, OND, CDER, FDA

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

February 15, 2017

Local Anesthetic Systemic Toxicity (LAST)

- LAST was first described in the late 1800's in association with cocaine
- Systemic toxicity continued to be a safety concern as new local anesthetics were developed
- LAST is related to elevated plasma levels of local anesthetic
  - Inadvertent intravascular injection
  - System absorption
- Presentation of LAST
  - Neurotoxicity: CNS excitation (seizures)
  - Cardiotoxicity: Cardiac depression (bradycardia, hypotension, conduction delays, cardiac arrest)
- Time course
  - Within one hour, with the non-extended-release local anesthetics
  - Unclear whether time course is influenced by liposomal preparation

Previous Safety Concerns: 2014 Submission

- Cardiac manifestations of BUP toxicity
  - Applicant did not fully analyze Holter monitor data
  - Monitoring was discontinued before mean Tmax in Study 323
- Neurologic manifestations of BUP toxicity
  - Questionnaire was discontinued before Tmax in Study 323
- Block onset and duration not characterized in FNB and nerve blocks in general
  - Falls only in the EXPAREL arms
  - Motor function evaluation (20-meter walk test with assist device) has low sensitivity and specificity for motor block
- No support for extrapolation of safety to all nerve blocks

2017 Submission: Additional Cardiac Data

- Applicant submitted re-analyzed Holter monitor and ECG data from Studies 322 and 323
- Division of Cardiovascular and Renal Products
  - No cardiac-related safety concerns with previous Holter data from Studies 322 and 323
  - No cardiac-related safety concerns from Studies 326 and 327

2017 Submission: Neurologic Data

- Neurologic questionnaire was continued beyond Tmax in both new studies (Studies 326 and 327)
- Multiple AEs that may be neurologic manifestations of LAST, however, no clear signal identified
  - Multiple confounders

2017 Submission: Block Characterization

- Study 326 (Femoral)
  - Sensory assessment on anterior thigh and in the foot (saphenous nerve distribution)
    - Cold, light touch and pinprick
  - Motor assessments
    - Active angle flexion and extension
- Study 327 (Brachial plexus)
  - Sensory assessments in shoulder
    - Cold, light touch, pinprick
  - Motor assessments in elbow and thumb
    - Elbow flexion, thumb abduction, thumb adduction

Study 326: Sensory Assessments

- Placebo
  - Anterior: 1 subject with deficit at 120 hours
  - Saphenous: All subjects return to baseline by 108 hours
- EXPAREL 133 mg
  - Anterior: 1 subject did not return to baseline until 120 hours
  - Saphenous: 3 subjects with sensory deficits at 120 hours
- EXPAREL 266 mg
  - Anterior: 4 subjects had persistent sensory deficits at 120 hours
  - Saphenous: 5 subjects with persistent deficit at 120 hour

Study 326:
Median Time to Loss of Sensation

	Time in Hours (95% CI)
Placebo	71.8 (6.3, 102.1)
EXPAREL 133 mg	5.8 (4.5, 6.4)
EXPAREL 266 mg	6.4 (4.1, 13.0)

Mean Tmax EXPAREL = 72 hrs

Study 326:
Median Time to Loss of Motor*

	Time in Hours (95% CI)
Placebo	11.8 (5.9, 36.7)
EXPAREL 133 mg	8.9 (6.5, 48.3)
EXPAREL 266 mg	6.3 (5.9, 9.1)

Mean Tmax EXPAREL = 72 hrs

*Missing appx 50% of subjects

Study 326: Time (hrs) to Return of Motor Function

	Statistic	EXPAREL 133 mg [N=75] n (%)	EXPAREL 266 mg [N=76] n (%)	Placebo [N=79] n (%)
Number of Subjects with				
Motor Function Return	n (%)	55 (73.3)	60 (78.9)	56 (70.9)
No Motor Function Return	n (%)	16 (21.3)	15 (19.7)	19 (24.1)
Time to Return				
Quartiles [1]				
First (25%)	Estimate (95% CI)	89.58 (75.02,101.75)	89.15 (62.28,96.82)	74.20 (50.67,94.97)
Median (50%)	Estimate (95% CI)	182.37 (102.02,262.20)	169.13 (104.50,291.02)	139.07 (95.80,216.38)
Third (75%)	Estimate (95% CI)	624.92 (262.20,663.25)	642.17 (333.17,673.13)	642.28 (216.38,699.25)
Minimum	Observed	0.33	0.00*	0.00*
Maximum	Observed	818.32	728.33	1022.87
p-value [2]		1.0000	1.0000	

Return (Flexion and Extension must return):
Flexion = angle $\geq 80°$ if baseline$\geq 80°$, otherwise post-baseline change $\leq -10°$
Extension = angle $\leq 10°$ if baseline $\leq 10°$, otherwise post-baseline change $\leq 10°$
* indicates censored observation
[1] Estimates from Kaplan-Meier analysis.
[2] p-value from log-rank test with terms for treatment comparing EXPAREL to placebo.

Source: Applicant's Study 402-C-326 Study Report; Table 34, Page 83

Falls

	Study 323 (Part 2)		Study 326		
Event	EXP 266 mg	PLB	EXP 133 mg + 40 mg BUP	EXP 266 mg + 40 mg BUP	PLB + 40 mg BUP
Fall	3	0	4	5	0

Study 327:
Median Time to Loss of Sensation

	Time in Hours (95% CI)
Placebo	71.8 (70.8, 72.4)
EXPAREL 133 mg	6.1 (4.6, 12.1)

Mean Tmax EXPAREL = 48 hrs

Study 327:
Median Time to Loss of Motor

	Time in Hours (95% CI)
Placebo	70.4 (11.9, 71.8)
EXPAREL 133 mg	6.1 (5.8, 9.2)

Mean Tmax EXPAREL = 48 hrs

Study 327:
Time to Return to Motor Function

- Radial Nerve/Ulnar Nerve
  - Placebo: All subjects had full return to motor function by 28 hrs
  - EXPAREL 133 mg: All subjects had full return to motor function by 42 hrs
- Median Nerve
  - Placebo: All subjects had full return to motor function by 108 hrs
  - EXPAREL 133mg: All subjects had full return to motor function by 42 hrs

Characterization of Block Onset/Duration: Summary

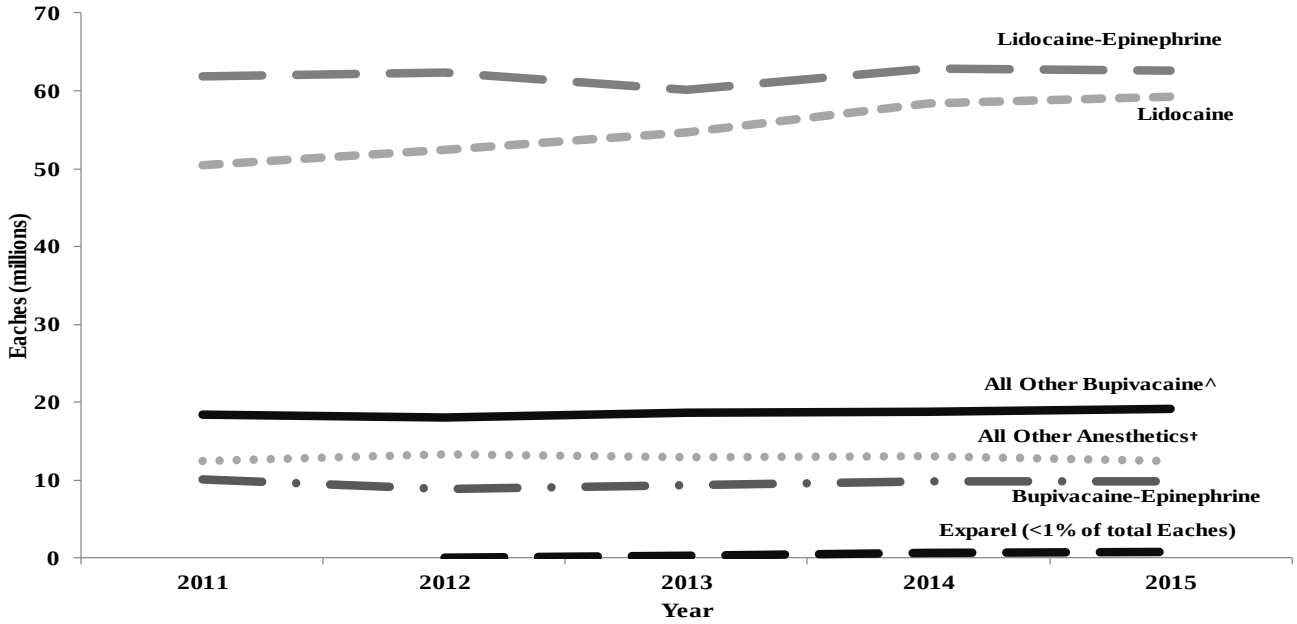
- New studies included focused sensory and motor function exams through Tmax and until resolution of the nerve block
  - Study 326
    - 50% of study population had missing motor exams in the first 48 hours due to immobilization
    - Adequately characterized sensory block onset and return
  - Study 327: adequately characterized motor and sensory block onset/return
- Significant variability at different anatomical sites
- Onset of sensory and motor loss did not correlated with Tmax
- As with previous FNB study (323), all falls in Study 326 were in the EXPAREL arms

LAST

Methods

- The FDA Adverse Event Reporting System (FAERS) database and medical literature were searched for LAST with Exparel or other local anesthetics (LAs)
  - FAERS search dates and terms
    - October 28, 2011 – November 8, 2017 – Exparel
    - July 1, 2006 – November 8, 2017 – LAs
    - System Organ Class: Cardiac disorders; nervous system disorders; respiratory, thoracic and mediastinal disorders
    - "Systemic toxicity" was searched in the report narrative
    - Serious outcomes: death, life-threatening, hospitalization, disability, congenital anomaly and other serious important medical events.
  - Literature search dates
    - November 15, 2006 – November 8, 2017

National sales* estimates (eaches**) of local anesthetic injectable products, by active ingredient, sold from manufacturers to various U.S. channels of distribution, years 2011-2015



Source: IQVIA, National Sales Perspectives. Years 2011-2015. Data Extracted July 2016.
***Total sales distribution of local anesthetics from manufacturers are underestimated because direct sales from manufacturers such as to dental offices are not captured**
****Eaches refer to the number of vials, ampules , syringes, cartridges, IV bags, or cassettes of a products shipped in a unit**
†Other Anesthetics include: Roipivicaine, Mepivicaine, Prilocaine, Prilocaine-Epinephrine, Chloroprocaine, Tetracain, Mepivacaine-Levonorderfrin, and Procaine
^ All Other Bupivicaine does not include Exparel; Exparel is shown as the lower most dashed line

Results of the DPV Review

- Total number of cases (n=111)
  - Exparel (n=39); LAs (n=72)
- Time to onset
  - Rapid onset LAST (≤ 1 hour): Exparel (n=10), LAs (n=63)
  - Delayed onset LAST (>1 – 96 hours)
    - 65 minutes to 72 hours – Exparel (n=11)
    - 80 minutes to 12 hours – LAs (n=3)
  - Not reported (n=24)
- 8 fatal cases (Exparel n=5, LA n=3)
- Clinical manifestations involved cardiovascular (e.g., bradycardia, hypertension) and central nervous system (e.g., seizures, respiratory depression) toxicity
- 24 LA cases reported suspicion or confirmed inadvertent intravascular administration; 1 case with Exparel
- Lipid emulsion administered in more than one-third Exparel cases (n=15) and more than half (n=47) of the LA cases

LAST Conclusions

- LAST occurs across the injectable LA class, with variable time to onset and clinical presentation.
- Clinical symptoms (i.e., cardiovascular, central nervous system) were similar among the Exparel and other LA cases and among the rapid and delayed onset cases.
- LAST may present minutes, hours or even days following LA administration depending on type of injection or infusion, LA dose, and the presence of other risk factors (e.g., age, renal dysfunction, hepatic dysfunction, cardiac disease, pregnancy, block site and technique).
- The language in the LA labels is variable in the description of LAST. None of the labels mention the risk of delayed onset of LAST.
- FDA will continue to monitor and determine if further regulatory action is needed.

Safety Summary

- Safety is based on local drug effects and systemic bupivacaine exposure (PK profile)
- Great variability in the PK profile of EXPAREL with different nerve blocks and administration techniques
- PK profile at sites that have not been evaluated is still unknown, and the Applicant has not provided a rationale to support extrapolation of the PK and safety data to other commonly performed nerve blocks
- No rationale provided on how to make appropriate dosing decisions for different types of nerve blocks
- Risk of delayed LAST is uncertain and needs further monitoring

U.S. FOOD & DRUG ADMINISTRATION

Questions?